

MAMMOGRAPHIC SCREENING FOR BREAST CARCINOMA

A Cross-sectional Randomized Study
of 45–69 Year Old Women

Ingvar Andersson



Lund 1981

Malmö 1980

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Ingvar Andersson
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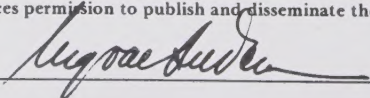
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Abstract In a randomized mammographic screening of 45-69 year old women breast carcinoma was demonstrated in 7.5 per thousand women at the first screening; 16% of the carcinomas were non-invasive and 43% invasive ≤ 10 mm. Axillary metastases were proven in 18%. The sensitivity of mammography was 91.5% and the specificity 99.2%. The sensitivity of mammography varied with the number of projections available, the size of invasive carcinomas and the age of the patients. It was concluded that 2 views of each breast should be obtained, at least at the first screening. The mammographic parenchymal pattern was classified according to Wolfe as either N1, P1, P2 or DY. The proportion of the supposed high-risk patterns P2 and DY decreased with the age at examination and increased with increasing age at first delivery and was highest among nulliparae. The relative risk of breast cancer in women with P2 and DY patterns compared with those with N1 and P1 patterns was 1.5. It was concluded that selective screening of women with P2 and DY patterns is not meaningful. The radiographic and pathologic appearance of tubuloductal carcinomas was compared. Small, highly differentiated tubular carcinomas were characterized by pronounced retraction of structures surrounding the lesion. With increasing size and decreasing differentiation the tumours tended to be more clearly circumscribed. The appearance of tubular carcinomas make them readily detectable by mammography which might explain the large proportion of such carcinomas in the screened population. Breast cancer detected at screening as well as cases detected in the entire study population during a 1-year follow-up were characterized regarding prognostic markers such as tumour size, axillary metastasis and histologic type. A comparison of the carcinomas appearing among the controls with those detected by screening revealed a significantly larger proportion of small carcinomas and carcinomas without axillary metastases in the latter group. The effect of length-biased sampling was discussed, especially regarding the hypothesis that tubular carcinoma represents an early stage of progression towards less differentiated ductal carcinoma. It was concluded that screening can be expected to have a substantial effect on the mortality from breast carcinoma.		
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Tord Olin), University of Lund, Malmö General Hospital,
S-214 01 Malmö, Sweden.

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"Mass screening surveys form one of the meeting points between epidemiology and clinical practice. The methods appropriate to mass examinations are epidemiological, but the objective is clinical action for individuals. Although both disciplines are involved each needs to face some basic differences from its more usual area of practice."

Barker & Rose, 1976.

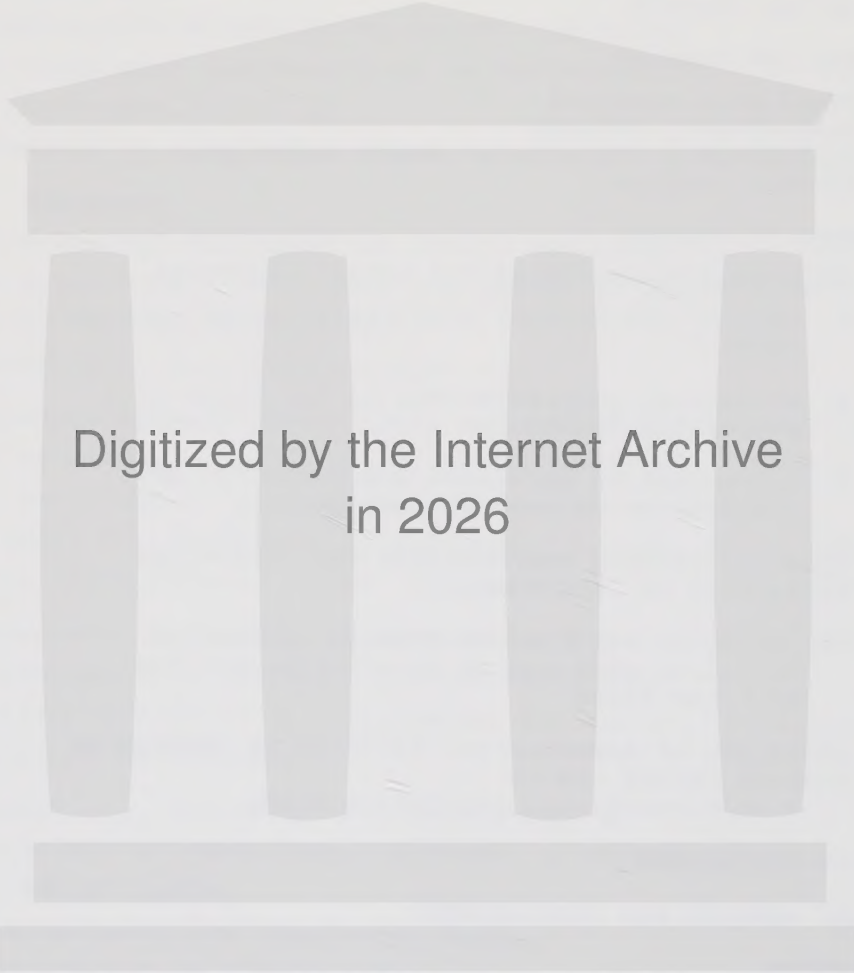
This thesis is based on the following papers:

- I. I. Andersson
MAMMOGRAPHIC SCREENING FOR BREAST CARCINOMA
1. Program and primary findings in 45-69 year old women.
Accepted by Acta Radiol Diagn
- II. I. Andersson
MAMMOGRAPHIC SCREENING FOR BREAST CARCINOMA
2. Prognostic considerations on the basis of
a short-term follow-up
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- III. I. Andersson
MAMMOGRAPHIC SCREENING FOR BREAST CARCINOMA
3. Appearance of carcinoma and number of projections
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- IV. Relation between mammographic and pathologic appearance
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APPRAISAL OF MAMMOGRAPHIC PATTERNS AS MARKERS OF RISK
OF BREAST CANCER.
A cross-sectional population study.
Submitted to Am J Epidemiol

These papers will be referred to in the text by their Roman numerals I - VI.

C O N T E N T S

INTRODUCTION	7
General background	7
Screening for breast carcinoma	8
Remarks on the evaluation of screening tests	9
Remarks on the evaluation of the effect of screening	10
AIMS OF THE PROJECT	12
MATERIAL AND METHODS	13
Population material	13
Radiographic methods	13
Radiographic criteria of breast carcinoma	14
General routine	14
SUMMARIES OF PAPERS	16
I. RADIOGRAPHIC SCREENING FOR BREAST CARCINOMA	
1. Program and primary findings in 45-69 year old women.	16
II. 2. Prognostic considerations on the basis of a short-term follow-up	19
III. 3. Appearance of carcinoma and number of projections to be used at radiography.	21
IV. RELATION BETWEEN MAMMOGRAPHIC AND PATHOLOGIC APPEARANCE OF CARCINOMA	23
V. RADIOGRAPHIC PATTERNS OF MAMMARY PARENCHYMA Variation with age at examination and age at first birth	27
VI. APPRAISAL OF MAMMOGRAPHIC PATTERNS AS MARKERS OF RISK OF BREAST CANCER A cross-sectional population study	29
GENERAL DISCUSSION	31
GENERAL SUMMARY AND CONCLUSIONS	41
REFERENCES	45
Paper I	51
Paper II	77
Paper III	93
Paper IV	Chapter XI (p. 199-217) in: BREAST CARCINOMA. Linell, Ljungberg and Andersson, 1980.
Paper V	121
Paper VI	135



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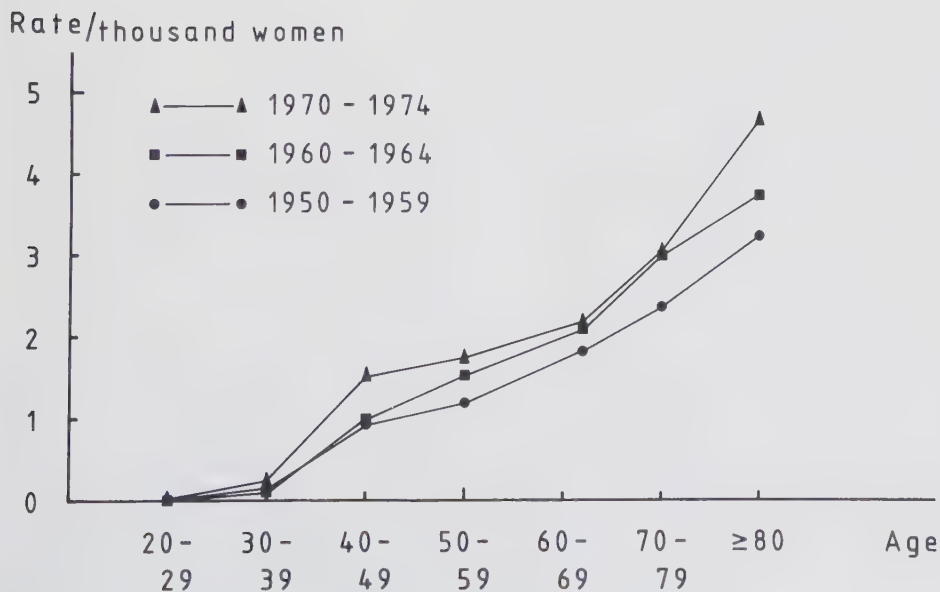
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INTRODUCTION

General background

Breast carcinoma is the most frequent malignant disease in Swedish women, comprising 24 % of all carcinoma in the female population (Cancer Incidence in Sweden 1974). Data from the city of Malmö indicate that the incidence rate has increased during the last decades (Fig.1). The observed increase is in accord with data from various parts of the world (Tulinus 1979). These data indicate an increase in incidence as well as in mortality rate in the

Fig. 1. Age specific breast cancer incidence in Malmö in three periods (1959 cases).



majority of countries studied. In 1974 the highest age standardized incidence rate within Sweden was reported from Malmö, 114.5 per 100 000 women, which was well above the average rate for the whole of the country, 85.5 per 100 000 women (Cancer Incidence in Sweden 1974).

Long-term follow-up studies of clinical series of patients with breast carcinoma have almost invariably shown that the prognosis varies with the size of the tumour at the time of treatment (Adair et al 1974, Say & Donegan 1974, Duncan & Kerr 1976, Wallgren et al 1976, Attiyeh et al 1977, Frazier et al 1977, Langlands & Kerr 1978), the smaller the tumour, the less the probability of metastasis and the better the prognosis. Kreyberg and Christiansen (1953) did not find "small" carcinomas (< 15-17 mm) to be associated with a particularly favorable prognosis. It would, however, appear reasonable to conclude that diagnosis and treatment of small tumours would improve the prognosis. This is the basic concept motivating mass examination of symptomfree women (screening) for carcinoma of the breast. In reality, the situation is not quite so straightforward and the knowledge of the effects of such a procedure far from complete.

Screening for breast carcinoma

Screening for carcinoma may be defined as the application of a test to a large number of people in order to identify individuals with and without the carcinoma in question and with the objective to reduce the morbidity and mortality from the carcinoma among the persons screened (slightly modified after Cole & Morrison 1978).

Several screening projects for the detection of breast carcinoma have been reported. Most projects have concerned groups of women preselected in one way or another (Gershon-Cohen et al 1961, Witten & Thurber 1964, Wolfe 1965, Rasmussen 1969, Dowdy et al 1971, Venet et al 1971, Stark & Way 1974, Chamberlain et al 1975, George et al 1976, Strax 1976, Frischbier & Lohbeck 1977, Feig et al 1977, Beahrs et al 1979), while ongoing projects in Sweden (Lundgren & Jakobsson 1976, Lundgren 1979 b, Fagerberg, Tabár &

Gad) and Holland (de Waard et al 1978, Rombach 1980, Hendriks) are population-based, i.e. a cross-section of the general female population, unselected except for age, is invited.

Some programs have set an upper age-limit, e.g. 64 years in the DOM-project (de Waard et al 1978) and 74 years in the BCDDP (Breast Cancer Detection Demonstration Project, Beahrs et al 1979), while others have not (Chamberlain et al 1975, George et al 1976, Lundgren 1979 b). In most projects screening was started around the age of 40, in the DOM-project, however, at 50 (de Waard et al 1978).

In the Swedish projects mammography is the only screening method. This applies also to the projects by Rasmussen (1969) and by Hendriks. In all other projects more than one screening method was used, usually physical examination and mammography. Some programs also included thermography, which, however, is of questionable value for the purpose of screening (Jakobsson et al 1975, Johansson et al 1976).

Remarks on the evaluation of screening tests.

The correct identification of women with and without breast carcinoma by mammography, i.e. its *sensitivity* and *specificity*, depends on a number of factors, e.g. the definition of abnormality indicating malignancy, the quality of the film and developing process used, the number of projections used and the skill of the radiologist. These factors all influence the *predictive value* of mammography, i.e. the likelihood that a woman with a positive mammogram is affected by breast carcinoma and that a woman with a negative mammogram is free of breast carcinoma. The predictive value will also vary with the intra- and interobserver variation of the interpretation of the mammograms. Furthermore, the predictive value of a positive test is highly dependent on the prevalence of the disease in question (Galen & Gambino 1975). Screening for a low-prevalence disease like breast carcinoma will, irrespective of sensitivity and specificity, produce an unexpectedly high number of false positives, i.e. women free of carcinoma with a suspected screening mammogram. This is important

to realize when planning screening. By repeating the screening mammography or by the addition of complete mammography to those initially suspected, the number of false positives can be reduced and thereby the need for further investigations, including surgical biopsy.

Another way to improve the predictive value would be to identify a high-risk group, thereby increasing the prevalence in the group to be screened. This would also increase the efficacy of the screening. Epidemiologic studies have shown that there are women at high risk, such as those with late first birth, and nulliparae and those with a family history of breast cancer (MacMahon et al 1970). However, the relative risk of these groups seems to be only moderate and not large enough to warrant selective screening (Soini 1977, de Waard et al 1978). In 1976 data were published by Wolfe indicating that certain parenchymal patterns (termed P2 and DY) as recognized on the mammogram, were associated with a substantially increased risk of breast cancer. If this is right, it will have profound implications for breast cancer screening with mammography. Later results have, however, not been unequivocal (Egan & Mosteller 1977, Mendell et al 1977, Rideout & Poon 1977, Egan & McSweeney 1979).

Remarks on the evaluation of the effect of screening

The main problems are those related to the evaluation of the effect of mammographic screening on the morbidity and mortality of breast carcinoma. As mentioned above, our knowledge of prognostic markers for breast carcinoma is based on symptom-diagnosed cases. There are, however, certain mechanisms operating in the screening situation which tend to bias comparisons between carcinomas detected clinically and at screening. The probability of a carcinoma being detected at screening varies with the length of its preclinical phase, which varies with its growth rate (Feinleib & Zelen 1969). This would mean that screening preferably picks up slow-growing tumours (length-biased sampling). Reasonably, a slow-growing tumour is less malignant than a rapidly growing one. Another factor, which has a profound bearing on

mammographic screening, is the kind of morphological changes produced by the "early" or preclinical malignant lesion. It is theoretically possible that carcinomas with a less than average grade of malignancy might produce such radiographic changes as make them more readily detectable and/or that carcinomas with a more than average degree of malignancy lack early radiographic characteristics making them less readily detectable. Theoretically, the situation might also be the opposite.

Another important point in the comparison of prognostic variables is the representativeness of the invited cohort vis-à-vis the general female population from which the clinical series are derived. Most reported screening projects are restricted to self-selected women, e.g. the multi-center study in the U.S.A. called BCDDP (Beahrs et al 1979). Only the Swedish (Lundgren 1979 b, Fagerberg, Tabár & Gad) and the Dutch (de Waard et al 1978, Hendriks) projects are population-based, i.e. a cross-section of the female population in a certain age-group was invited to screening. Clearly, there is a substantial possibility of biased sampling in the self-selected type of population. However, also in a population-based project a low attendance rate might imply a selectivity, leading to a biased sample of carcinomas. Another factor which must be accounted for if the evaluation is based on a comparison of case-fatality rates, is the lead-time of the screening cases, i.e. the time between diagnosis with the screening program and the usual time of diagnosis under current medical practice. At present there is no method to adjust for lead-time.

Many of the above difficulties may be avoided by conducting a randomized trial. A comparison of the mortality between the group invited to screening and their controls will give an estimate of the benefit of screening. However, there are problems associated also with a randomized trial. A large study population must be followed for a long period of time, while consequent loss of patients in the trial due to migration and deaths from causes other than breast cancer. Although results from several screening projects have been reported, only one was designed as a controlled trial, the so-called HIP-study (Health Insurance Plan of

Greater New York). In the HIP-study annually repeated screening of 50-64 year old women with physical examination and mammography reduced the mortality by about 30 %, while no such effect was demonstrated in 40-49 year old women (Shapiro 1977, 1978). It is not known to what extent mammography had contributed to the reduction (Breslow et al 1977, Thomas et al 1977). Furthermore, the HIP-study was conducted in the 1960's, since when the diagnostic capacity of mammography has improved substantially.

In the light of the above considerations it seemed that further investigation of problems related to breast cancer screening with mammography was warranted. It also appeared that the fundamental question of the long-term effect of mammographic screening could be answered only by a randomized, controlled trial.

AIMS OF THE PROJECT

The purpose of the present project was to set up a centre for screening for breast carcinoma as a public health service, which could also provide a basis for research. The main purpose of the long-term perspective is to assess the impact of mammographic screening on the morbidity and mortality of breast carcinoma in 45-69 year old women.

The aims of the present thesis were:

1. To assess the breast cancer detection rate in relation to age in an urban, cross-sectional sample of 45-69 year old women.
2. To study the validity of mammography in relation to tumour size and number of projections used.
3. To analyse the radiographic characteristics of carcinomas detected at screening.
4. To characterize cases detected at screening and symptom-diagnosed cases in terms of prognostic markers such as tumour size, axillary metastasis and histologic type of carcinoma.

5. To estimate the validity of the parenchymal classification system of Wolfe (1976 a,b) for the purpose of selective screening.
6. In the course of the work evidence was accumulating that the so-called radial scar could develop into tubuloductal carcinoma. A study was undertaken to compare the radiographic and pathologic appearance of the radial scar developing into tubuloductal carcinoma.

MATERIAL AND METHODS

Population material

A 50 % random sample (n = 21,242) of all 45-69 year old women living in the city of Malmö were invited to breast cancer screening with mammography. The remaining 50 % (n = 21,240) served as a control group, which was not screened. The material was obtained from the population registry of the city. The randomization was done by a computer.

Radiographic methods

Mammography was the only screening test used. The X-ray unit was a Philips Diagnost M which was operated at 28 kV (25 kV at the second screening). One craniocaudal and one oblique projection were obtained of each breast. In the oblique projection the tube was tilted about 45° medially, and the woman was placed in such a way that the mammogram included the breast and as much as possible of the axilla. Most of the examinations of the first screening were performed with the Kodak Min-R screen-film system and Agfa Gevaert MR 50 screens combined with Scopix film. At the second screening Kodak Min-R screens combined with Kodak NMB-film were used. The films were developed at 31°C, developing time 57 seconds, total processing time 4.5 minutes. The developer used was G 137 (Agfa Gevaert). The mean absorbed dose was 1 mGy per exposure, as measured with thermoluminescent dosimeters.

Radiographic criteria of breast carcinoma

The following abnormalities were considered to suggest carcinoma and constituted the selection criteria for complete mammographic examination.

1. A *tumour mass* with an irregular or poorly defined border with or without retraction of tissue strands towards the tumour. Also a rounded, nodular or lobulated tumour mass, mainly well delineated but poorly defined in some part of the periphery, was suspected of being carcinoma. Although not decisive the density of a tumour was also taken into account, high density indicating malignancy.
2. Distortion of the normal architecture of the breast, usually in the form of *retraction* of the structures in a stellate manner, but without a dominating tumour mass.
3. Irregular *calcifications*, i.e. calcifications of varying form and size, arranged either disorderly or in a linear fashion, and either appearing in one or more clusters or dispersed in one or more segments of the breast. Obviously benign, irregular calcifications, such as those occurring in plasma cell mastitis, fibroadenoma and in the arterial walls, were not included in this group.

Notes were also made of any thickening or retraction of the skin and nipple.

General routine

When nothing suggestive of malignancy was observed on the screening films, no further examination was done. If abnormalities suggestive of carcinoma were observed on one or both views, the woman was recalled for complete mammographic examination, implying in most cases one or more films in the craniocaudal, oblique and lateromedial projections and, when indicated, coned-down views. If the complete mammography dispelled the suspicion, the woman was immediately informed and sent home. But if it did not, the patient was immediately referred for physical examination followed by fine needle aspiration biopsy. Patients with suspect

findings at complete mammography were discussed by a team consisting of one radiologist, one cytologist, one oncologist, one pathologist and one surgeon at weekly conferences. Surgical biopsy was invariably recommended except in cases where the mammographic findings were very uncertain and physical examination as well as fine needle aspiration biopsy had revealed nothing remarkable. In these cases the women were kept under observation. If fine needle aspiration biopsy, mammography and physical examination had clearly shown carcinoma, mastectomy was done without surgical biopsy.

The standard treatment for invasive carcinoma was modified radical mastectomy and for carcinoma in situ, simple mastectomy or subcutaneous mastectomy.

To assess the presence of distant metastases a roentgenogram of the chest was obtained of all patients with carcinoma. Patients with invasive carcinoma were subjected also to skeletal scintigraphy and radiography.

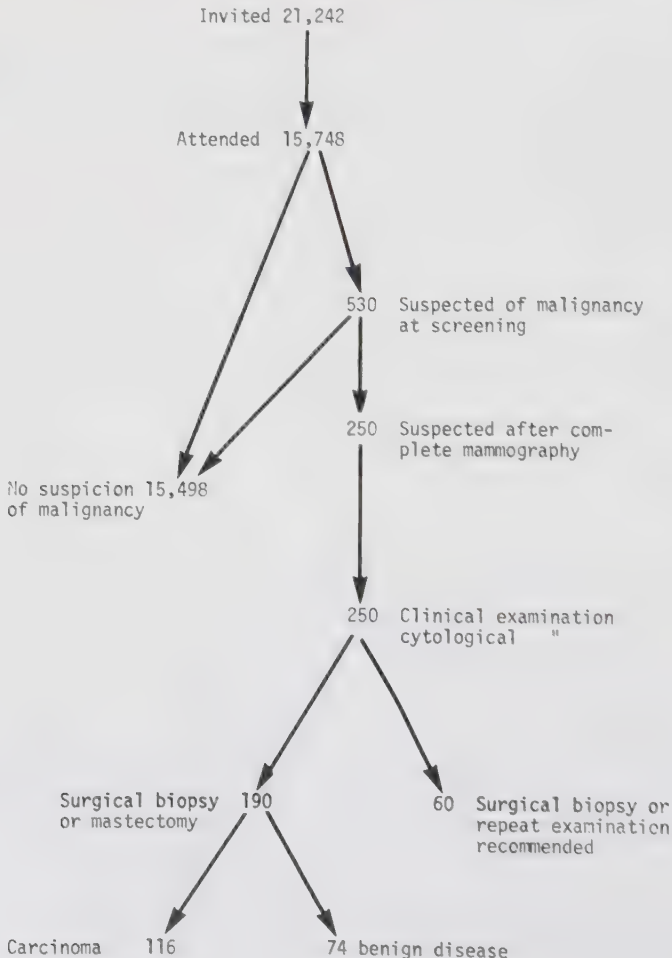
SUMMARIES OF PAPERS I - VI

RADIOGRAPHIC SCREENING FOR BREAST CARCINOMA

Primary findings (I).

Results. The results of the first screening are summarized in Fig. 2. 15,748 women attended the screening, corresponding to an attendance rate of 74 %. The rate was highest, 79 %, in the 45-54 year group, decreasing to 64 % in the 65-69 group. The screening films suggested malignant lesions in 3.4 % (530) of the participating women, but subsequent complete mammography reduced the figure to 1.6 % (250). Of these, 190 were operated upon, corresponding to 1.2 % of the women screened.

Fig. 2. Schematic representation of the project.



Carcinoma was histologically verified in 0.74 % (116). In addition, two women, who refused operation but who had radiographically typical carcinoma verified by fine needle aspiration biopsy were included, making a total of 118 women with carcinoma (0.75 %, table 1). Benign lesions were histologically verified in 0.47 % (74) of the screenees. Epithelial proliferations with atypia were found in 9 % of the benign biopsy specimens and radial scars (Linell et al 1980) in 12 %. Generally, the cancer detection rate increased with age, from 4.7 ‰ in the age-group 45-49 to 11.6 ‰ in the 65-69 group. Sixteen per cent (19) of the carcinomas were non-invasive and 43 % (51) were invasive and had a diameter of at most 10 mm. Axillary metastases were histo-

Table 1. Detection rate of breast carcinoma by age. Figures within brackets denote rate per thousand within each age group.

	Carcinoma in situ	Invasive carcinoma		Total
		≤ 10 mm	> 10 mm	
45-49	2 (0.7)	7 (2.3)	5 (1.7)	14 (4.7)
50-54	4 (1.2)	10 (2.9)	9 (2.6)	23 (6.7)
55-59	2 (0.6)	8 (2.3)	11 (3.1)	21 (6.0)
60-64	3 (1.0)**	14 (4.5)	12 (3.9)***	29 (9.3)
65-69	8 (3.0)	12 (4.5)*	11 (4.1)	31 (11.6)
45-69	19 (1.2)	51 (3.2)	48 (3.0)	118 (7.5)

* Diagnosis based on radiography and cytology in one patient in respective group.

** One patient treated for invasive carcinoma of the contralateral breast 12 years previously: no metastasis

*** One patient treated for carcinoma of the contralateral breast 14 years previously: no metastasis.

logically demonstrated in 6 % of the women with invasive carcinoma $\leq$ 10 mm and in 38 % of those with larger tumours.

Of those suspected at the complete mammography, 58 were not operated upon. In the majority of these cases (49/58) the suspicion could be dispelled at a follow-up within 6 months.

Taking the number of malignant tumours appearing within one year of a negative screening examination ($n = 11$) as a measure of false negatives the sensitivity of the screening procedure was 91.5 %. The specificity of the screening mammography was 97.4 %. Supplementary complete mammography increased the specificity to 99.2 %. The predictive value of a suspected mammogram at screening was 22.3 %. The predictive value of a positive complete mammography was 47.2 %.

RADIOGRAPHIC SCREENING FOR BREAST CARCINOMA

Prognostic considerations (II).

Methods: All cases of breast carcinoma appearing in the study population (invited group plus control group) within one year of the date of entry into the screening program were recorded.

Tumour size was determined by taking the longest diameter, measured on unfixed specimens (Linell et al 1980). In 6 cases tumour size was determined on the mammograms. Also, for staging according to the TNM-classification (UICC 1978), the T (tumour) and N (nodal) categories were determined from the pathologist's report. Exceptions were the above mentioned patients, whose tumours were measured on the mammograms, and 7 inoperable patients in whom clinical staging was done. Furthermore, the nodal status of 13 patients with non-invasive and 9 with small invasive carcinomas was assessed by palpation (all negative).

The histologic classification of carcinoma used was that proposed by Linell et al (1980). The material of Linell et al (1980) was used in the study of the distribution of histologic types of carcinoma. The cases detected at screening were compared with all the other women in the birth-cohorts 1908-1932 in whom breast carcinoma had been diagnosed in 1976-1978.

Unless otherwise stated, Chi-square test was used in the statistical comparisons.

Results. Breast carcinoma was detected in 118 women at the first screening, corresponding to 7.5 per thousand examined. During the 1-year follow-up carcinoma was diagnosed in 2.4 per thousand in the control group, in 0.7 per thousand in the screened group and in 3.3 per thousand in the group of non-participants. The detection rate at screening was significantly higher than the incidence rate in the control group ($p < 0.005$). The incidence in the screened group during the first year after screening (interval carcinomas) was significantly lower than the incidence in the control group ($p < 0.005$).

There was a significantly larger proportion of non-invasive carcinoma and invasive carcinoma with a diameter of at most 10 mm in the group of carcinomas detected at the first screening than in the control group ($p < 0.005$). The proportion of non-invasive carcinoma and invasive carcinoma with a diameter ≤ 10 mm was even larger at the second screening, 70 per cent, compared with 59 per cent at the first screening. The difference was not statistically significant. The median size of invasive carcinoma detected at the first screening was 8 mm compared with 20 mm in the control group, 25 mm in the group of non-participants, and 17 mm in the interval carcinomas.

A significantly lower rate of axillary metastasis was found in the group of carcinomas detected at the first screening compared with that in the control group, 21 and 47 per cent, respectively ($p < 0.005$). Though not statistically significant, the proportion of small invasive carcinoma with metastasis was larger at the second screening than at the first, 20 and 6 %, respectively.

The proportion of stage I disease was significantly larger in the group detected at screening than in the control group, 76 and 29 %, respectively ($p < 0.005$). When the entire invited group was compared with the control group, there was still a significantly larger proportion of stage I disease in the former group. The proportion of advanced disease (stage III and IV) was larger among non-participants than in the other groups ($p < 0.005$).

The proportion of non-invasive carcinoma was significantly larger in the group of carcinomas detected at screening than in the clinical series used for comparison, 16 and 8 %, respectively ($p < 0.025$). This applies also to tubuloductal carcinoma* which was due to a much larger proportion of well differentiated tubular carcinoma in the screening series, 35 %, compared with 15 % in the clinical series. Ductal carcinoma of "comedo" type as well as medullary carcinoma with lymphoid infiltration was significantly more common in the clinical series ($p < 0.001$).

* For histological classification, see Linell et al 1980, p. 120.

RADIOGRAPHIC SCREENING FOR BREAST CARCINOMA.

Appearance of carcinoma and number of projections to be used at radiography. (III).

Material and methods. The mammograms of 117 out of 118 patients with carcinoma detected at the first screening were reviewed to find out which of the following abnormalities was the most important sign of malignancy: 1. Tumour mass 2. Retraction 3. Calcifications (see Radiographic criteria of breast carcinoma page 14).

Furthermore, the visibility of these abnormalities in the various projections used was assessed and graded according to the following scale: Score 0 = no sign of malignancy, score 1 = uncertain sign of malignancy, score 2 = suggestive or frank sign of malignancy.

To test observer variation of the grading of the visibility the screening films were reviewed also by 2 other radiologists experienced in mammography. To prevent information from one projection facilitating interpretation of the other, the films were arranged so that the craniocaudal and the oblique projections of a given patient were not reviewed consecutively. The films of the women with cancer were intermingled with those of 100 randomly selected women without.

Results

Dominating abnormality suggesting malignancy

A *tumour mass* was the most important radiographic abnormality suggesting carcinoma in 58 % (68) of the patients with carcinoma. It was the dominating abnormality in 50 % of the invasive carcinomas with a diameter $\leq$ 10 mm and in 88 % of invasive carcinomas $>$ 10 mm.

Retraction was the dominating abnormality in 11 % (13) of the cases. Ten of the cases were invasive carcinomas $\leq$ 10 mm and 3 were $>$ 10 mm.

Calcifications were the main abnormality in 31 % (36) of the cases. Eighteen of these 36 cases were non-invasive carcinoma, 15 cases invasive ≤ 10 mm and 3 invasive > 10 mm. Thus, 95 % of the non-invasive carcinomas were betrayed mainly by calcifications, as were 30 % of invasive carcinomas ≤ 10 mm and 6 % of invasive carcinomas > 10 mm.

Visibility

Considering the screening films only, 8 % of the carcinomas were considered not visible (score 0) in the craniocaudal projection and another 3 % uncertain (score 1). The corresponding figures for the oblique projection were 6 % and 3 %. Generally, the reviewers classified a larger proportion accordingly.

There was a correlation between the size of invasive carcinoma and its visibility. Thus, 16 % of invasive carcinomas ≤ 10 mm were not visible in the craniocaudal projection and 4 % were uncertain. The corresponding figures for invasive carcinomas > 10 mm were 2 % and 4 %, respectively. In the oblique projection 10 % of invasive carcinomas ≤ 10 mm were not visible while 4 % were uncertain. The corresponding figures for invasive carcinomas > 10 mm were 4 % and 2 %, respectively. Essentially, the same results were obtained when not only the screening films but also the films taken at the complete mammographic examinations were considered.

The age distribution of patients with a score of 0 or 1 in at least 1 film was studied. The proportion of such patients varied with age, decreasing from 43 % of the patients with carcinomas in the age-group 45-49 to 10 % in the 65-69 year group.

The major reason why a malignant tumour was difficult or impossible to identify was superimposition of dense tissue or un-specific appearance of the tumour, not differing from the parenchyma (23 cases). Only occasionally (4 cases) was it because the tumour was situated juxtathoracically and therefore not included in the radiogram.

RELATION BETWEEN MAMMOGRAPHIC AND PATHOLOGIC APPEARANCE OF CARCINOMA (IV).

This work was prompted by the observation that retraction (spicules) were often abundant around radiographically detected "radial scars" and small tubuloductal carcinomas*. With increasing size (and decreasing degree of differentiation) of tubuloductal carcinomas the retraction tended to be less conspicuous and the tumour mass to be more clearly circumscribed.

Material and method. To study the correlation between the histologic and radiographic appearance of the tumour periphery 122 patients representing consecutive cases of breast carcinoma in the birth-cohorts 1908-1932, seen during 1978, were reviewed. Fifteen cases were excluded because calcifications were the only radiographic abnormality, 4 because the lesions were radiographically occult and 3 because the lesions could not be classified histologically. This left 100 cases, 36 of which had been discovered at screening. The remaining 64 had presented with clinical symptoms.

The degree of retraction was subjectively classified as follows:

- +++ : Long tissue strands extending from the entire circumference of the tumour
- ++ : Tissue strands of moderate length extending from the entire circumference.
- + : Tumour mainly or partly well defined but with small spicules discernible in some part of the periphery
- : No retraction.

Results

63 out of 100 carcinomas were classified as tubuloductal. Twenty (95%) out of 21 well differentiated tubuloductal carcinomas showed pronounced or moderately pronounced retraction (+++ and ++), compared with only 24 (57 %) out of 42 less differentiated

* For nomenclature and classification see Linell et al 1980, p.120.

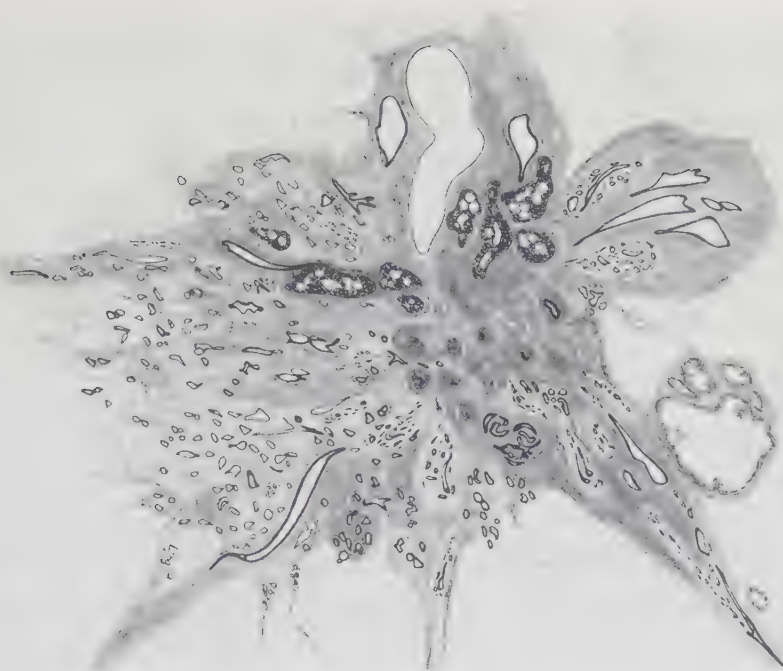
tubuloductal carcinomas. Forty (78 %) of 51 tumours at most 2 cm across and with pronounced or moderate retraction were tubuloductal compared with 12 (48 %) of 25 with inconspicuous or no retraction.

A well differentiated tubular carcinoma and a radial scar were both characterized by pronounced retraction of surrounding structures and radiographic differentiation between them was virtually impossible. It emerged from histological studies (Linell et al 1980) that, when tubular carcinomas progressed to larger, less differentiated tumours, the growth in the propagation zone was most pronounced in the fatty tissue between the spicules with the result that the tumour tended to have a more rounded, smooth contour (Fig. 3 a-c).

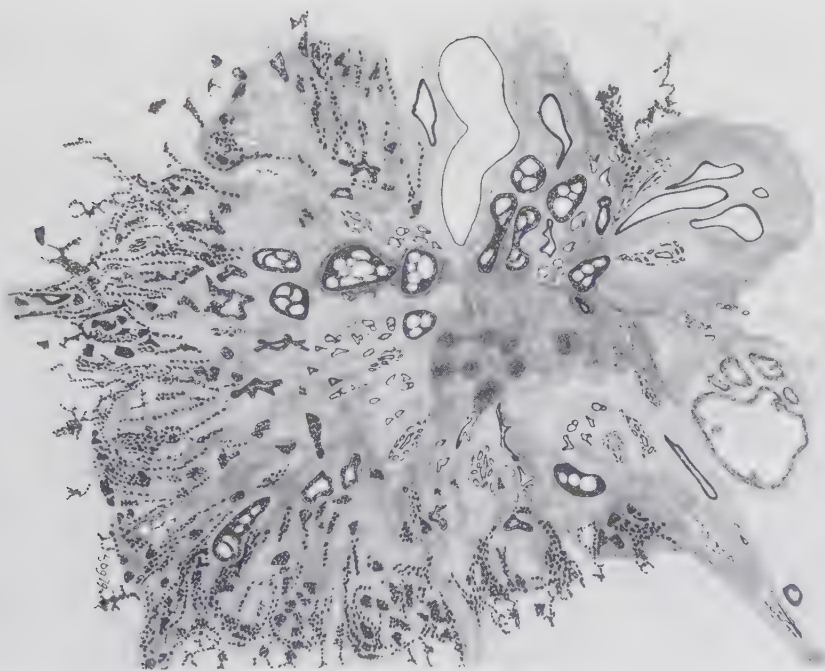
Fig. 3. Schematic drawings of tumour progression.



A. Radial scar with sclerotic centre with elastoid material and a few tubules. The centre is surrounded by spicules containing stretched, radially arranged ducts and lobules.



B. Pure tubular carcinoma. In the left part infiltration of tubules out into fatty tissue.



C. Progression to less differentiated carcinoma. Especially in the lower and left parts proliferation of less differentiated cell columns filling the spaces between spicules are demonstrated.

Comments. The striking radiographic similarity between radial scars and tubular carcinomas lends support to the hypothesis that radial scars can develop into tubular carcinoma (Linell et al 1980). The fact that tubular carcinoma, even in its earliest stage, is characterized by pronounced retraction facilitates its detection by mammography. This might in part explain the overrepresentation of tubular carcinoma in screened materials compared with clinical materials. In our screened series pure tubular carcinoma constituted 21.5 % of all carcinomas, while in our clinical series 6.7 % were pure tubular (II). It should be noted that our clinical series included some clinically occult cases, detected by mammography.

Patchefsky et al (1977) reported tubular carcinoma in 9 % of their screening series. The corresponding figure for clinical materials is 1-2 % (Fisher et al 1975, Rosen 1979). Histologic and statistical studies strongly indicate that tubular carcinoma progresses to less differentiated ductal carcinoma (Linell et al 1980). This can probably explain why the proportion of tubular carcinoma is so large in materials collected by mammographic screening.

The opinion of Hamperl (1968) and others that spicules (called retraction above) are signs of stellate outgrowths from a carcinoma seems to be essentially wrong. The spicules are evidently formed by retraction of structures surrounding the lesion. The spicules seen in radial scars are free from carcinoma. This also applies to many tubular carcinomas. Sometimes, tumour formations can grow into the spicules, although, as illustrated above, the growth occurs mainly between the spicules.

RADIOGRAPHIC PATTERNS OF THE MAMMARY PARENCHYMA.

Variation with age at examination and age at first birth (V).

Material and methods. The investigation was based on 15 110 of 15 748 (96 %) women attending the first screening. The missing 638 cases could either not be classified owing to mammoplasty or were not available in the files at the time when data were being fed into the computer. When attending the screening the women were asked about their age at first delivery.

The mammograms were classified according to Wolfe (1976 a,b) at the primary interpretation of the screening films. The classification was done without knowledge of the woman's age at first birth. Breasts composed entirely or almost entirely of fat were classified N1. Breasts with linear and nodular densities (called "prominent duct pattern" by Wolfe) were classified P1 if at most 25 % of the breast volume was involved and P2 if more than 25 % was involved. Breasts dominated by confluent densities with or without a prominent duct pattern were classified DY.

The association between mammographic pattern and age at examination and age at first birth, respectively, was expressed as the odds ratio (Fleiss 1973). Statistical significance was assessed by Chi-square test.

Results: Combining N1+P1 and P2+DY the percentages in the whole population were 49 and 51 %, respectively. The percentage of mammograms classified as P2 and DY diminished from 66.2 % in the 45-49 year group to 41.5 % in the 65-69 group. Using the 65-69 year group as a reference, the odds of having the P2 or DY pattern varied according to age at first birth, from 0.9 to 1.7 in the 60-64 year group, from 1.2 to 1.8 in the 55-59 year group, from 1.3 to 2.5 in the 50-54 year group and from 2.2 to 4.7 in the 45-49 year group.

The proportion of mammograms classified as P2+DY increased with increasing age at first birth and was highest among nulliparae. Using women with first birth before 20 as a reference group, the

odds of having the P2 or DY pattern varied depending on age at examination from 1.4 to 1.8 in women with the first birth between the age of 20 and 32, from 1.8 to 3.1 in women with first birth after 32 and from 3.3 to 4.6 in nulliparae.

Comments. The material represented 71 % of a random sample of the population in the age-group in question. The main part of the missing 29 % were those who did not attend the first screening. No complete information was available on this group. However, the parenchymal pattern of those women from this group who attended the second screening did not differ from those attending the first. It therefore seems reasonable to assume that the results represent a good estimate of the general female population.

APPRAISAL OF MAMMOGRAPHIC PATTERNS AS MARKERS OF RISK OF BREAST CANCER (VI).

Material and method. The population material was identical with that described in paper V, as was the classification of the breast parenchyma. The parenchymal classification of 118 women with carcinoma detected at the first screening (I) was compared with that of women without carcinoma. The breasts of 18 patients belonging to the group of non-participants and appearing with breast carcinoma within one year of the invitation to screening were classified according to Wolfe (1976 a,b).

Statistical methods. Fisher's exact test was used for comparison of proportions. The odds ratio was calculated according to Fleiss (1973) and was used to express the magnitude of association between P2+DY patterns and breast cancer. The attributable risk was calculated according to the method by Levin (1953) using the odds ratio as an estimate of the relative risk of breast cancer associated with the P2 and DY patterns.

Results. The P2 and DY patterns were found in 51 % of all the participants and in 61 % of the women with breast carcinoma detected at screening ($p < 0,05$, Table 2). In the group of women who had been invited to screening but not participated, the P2 and DY patterns were found in 12 (67 %) out of 18 patients with breast cancer ($p > 0.05$ when compared to the prevalence of P2 and DY in participants with breast cancer).

The prevalence of the P2 and DY patterns decreased with age in the whole group of participants as well as in the subgroup with breast cancer. However, in all the age-groups the P2 and DY patterns were more common in women with breast cancer than in those without. The relative risk of breast cancer (as estimated from the odds ratio) in women with the P2 or DY patterns compared with women with the N1 or P1 patterns ranged from 3.1 in the 45-49 year-group to 1.3 in the 50-59 year group and 1.8 in the 60-69 year group.

Table 2 Relative and attributable risk of breast cancer associated with the P2 and DY mammographic breast patterns. Figures within brackets denote the percentages of P2+DY and P1+N1, respectively.

Age	Mammo- graphic pattern	Participants in breast cancer screening			Odds ratio	Attributable risk
		All participants	Women without cancer	Women with cancer		
45	P2+DY	1855 (66)	1843	12 (86)	3.1	58%
	P1+N1	947 (34)	945	2 (14)		
49						
50	P2+DY	3397 (52)	3371	26 (59)	1.3	13%
	P1+N1	3166 (48)	3148	18 (41)		
59						
60	P2+DY	2456 (43) ^x	2422	34 (57) ^x	1.8	25%
	P1+N1	3289 (57)	3263	26 (43)		
69						
45	P2+DY	7708 (51) ^x	7636	72 (61) ^x	1.5	20%
	P1+N1	7402 (49)	7356	46 (39)		
69						

^x p < 0.05

The overall risk of breast cancer that could be attributed to the P2 and DY patterns was 20%. It ranged from 58% in the 45-49 year-group to 13% in the 50-59 year-group and 25% in the 60-69 group.

Comments. No significant difference was found between participants and non-participants with cancer regarding the prevalence of the P2 and DY patterns. Thus, it is reasonable to assume that the cancer patients detected at screening were representative of all women with breast cancer in the invited cohort in terms of mammographic pattern. The representativeness of the screened group vis à vis the general female population was discussed in the previous paper (V).

GENERAL DISCUSSION

It seems that breast carcinoma fills several of Wilson & Jungner's (1968) criteria for a disease to be suitable for screening.

Breast carcinoma is a common disease which causes a considerable morbidity and mortality. There is evidence that morbidity as well as mortality has increased during the last few decades. Furthermore, breast carcinoma is, on the average, a rather slow-growing tumour (Hermanutz et al 1975, Fournier et al 1976, Lundgren 1977, Fournier et al 1980) with a presymptomatic stage long enough to permit the time of diagnosis to be substantially advanced through screening.

For a screening program to be successful there must be a simple, safe and sensitive screening test. There is vast evidence that mammography can reveal breast carcinoma at a pre-symptomatic and non-palpable stage. There is also a substantial number of reports on breast cancer detection programs using mammography (Gershon-Cohen et al 1961, Witten & Thurber 1964, Wolfe 1965, Dowdy et al 1971, Venet et al 1971, Stark & Way 1974, Chamberlain et al 1975, George et al 1976, Strax 1976, Feig et al 1977, Edinburgh Breast Screening Clinic 1978, Beahrs et al 1979 and others). In most programs, however, mammography was used together with physical examination and the independent contribution of each modality is not always clear.

In the BCDDP (Beahrs et al 1979) about 7% of the carcinomas were revealed by physical examination alone and 44 % by mammography alone (first screening). Out of "minimal" cancers (defined as non-invasive and invasive with a diameter of at most 10 mm) 9 % were detected by physical examination only and 55 % by mammography only. At the second screening the corresponding figures were 4 and 68 %, respectively. There was a remarkable variation between the participating institutions, the proportion of carcinomas detected by physical examination alone varying between 0 and 24 %. Feig et al (1977) and Chamberlain et al (1975) found that respectively 22 % and 19 % (4/21) of the carcinomas were detected by physical examination alone. The corresponding figures

for mammography alone were 43 % and 38 % (8/21), respectively.

The results reported by Langeland (1970), who used physical examination as the only screening modality, did not indicate that the time of diagnosis was substantially advanced through screening.

Cases detected by mammography have generally proved to be in an earlier stage than those detected by physical examination (Chamberlain et al 1975, Feig et al 1977, Beahrs et al 1979).

Lundgren used mammography as the only screening method. Extensive experience with this single modality approach led to the conclusion that it is a satisfactory method for breast cancer screening (Lundgren & Jakobsson 1976, Lundgren 1979 a, b).

During the preparation of this text a most important contribution to the knowledge of the accuracy of physical examination and mammography as screening tests was published (Rombach 1980). In the so-called DOM-project, which is a cross-sectional study of women, aged 50-64 and living in the city of Utrecht, mammography as well as physical examination is used at screening. Out of 111 carcinomas detected at the first screening, only one was revealed by physical examination alone. Fifty-eight per cent were detected by mammography only. Furthermore, the proportion with proven negative nodes was 46 % among cases detected by physical examination, while it was 13 % for cases detected by mammography only. Although it could not be stated explicitly that the two screening tests were used completely independently, the contamination seems to have been very small.

The sensitivity of mammography in the DOM-project was 95 % and the specificity 99 %. The sensitivity of physical examination was 41 % and the specificity 97 %. The predictive value of a recommendation for biopsy was 40 % for the entire screening procedure. Although the sensitivity of the present project was somewhat lower, 91.5 %, the figures of the DOM-project are in good agreement with ours (I).

The large differences between the reported contribution of respectively physical examination and mammography can be explained in several ways. Generally, very sensitive mammography will leave few carcinomas to be detected by physical examination alone, while less sensitive mammography will leave a large proportion. The sensitivity of a diagnostic method like mammography varies with the skill of the examiner and with all factors influencing image quality. It was shown in paper III that the sensitivity of mammography varies with the number of projections, especially regarding invasive carcinomas with a diameter of at most 10 mm. It also varies with the criteria of a positive test, or expressed in another way, with the degree of abnormality which is considered necessary to arouse suspicion of malignancy. Such criteria of abnormality may be difficult to define. Furthermore, they may be subject to variation with factors such as the mood of the radiologist. Recent underdiagnosis may, for instance, tend to turn a "misser" of tumours into a "maker" resulting in a temporary increase in the number of false positives.

Another variable influencing the sensitivity is the composition of the population screened. In the present series the relative amount of dense (fibroglandular) tissue, as observed on the mammogram, decreased with increasing age of the women and increased with increasing age at first birth, and was largest among nulliparae (V). It is a common experience that the detection of a carcinoma is more difficult in a dense breast than in a fatty one. This is also illustrated by the fact that all interval carcinomas in the present series, appearing within one year of the first screening, occurred in dense breasts (classified as P2 or DY). Also, the incidence of interval carcinomas was highest in the youngest age-group (II). The analysis of the visibility of carcinomas in relation to age (III) further illustrated this point, proportionally more carcinomas being difficult to identify in young age. Thus, age seems to be one factor influencing the sensitivity of mammography. In a screening population with predominance of young women the sensitivity of mammography will therefore be smaller than in a population consisting mostly of elderly women. In the BCDDP 48 % of the participants were below

the age of 50, while in the DOM-project none was below 50. In the present project 19 % were below 50.

One might imagine that also hormonal and environmental factors, for instance, might influence the appearance of the breast parenchyma. If so, there might be differences in the radiographic appearance of the breast between countries and even within countries, affecting the sensitivity of mammography.

A screening project is a compromise in which the ambition to detect as many diseased individuals as possible has to be weighed against the negative effects, psychological and physical, of false positive tests. Sensitivity and specificity are mutually dependent, both varying with the criteria of a positive test. It may be questioned whether every measure should be taken to increase the sensitivity if the specificity is thereby reduced. Principally, specificity is the most important factor as it affects the vast majority of the study population, while sensitivity affects only a small proportion of it (Cole & Morrison 1978).

The sensitivity and specificity may be changed by changing the criteria of a positive test, furthermore by technical changes of the screening test or by the addition of another test of the same or other type. Changing the criteria of a positive diagnosis, inevitably influences specificity. Lowering the level of positivity results in an increased sensitivity and a decreased specificity. In principle, technical improvements increase sensitivity as well as specificity. The results of the present investigation indicate that the use of 2 projections at screening increased sensitivity as well as specificity as compared with one projection (III). By the addition of complete mammography to all those who were suspected of carcinoma on the basis of the screening films the specificity was increased from 97.4 to 99.2 % (I). The number of false positives was reduced from 410 to 132, i.e. by 278 women at the price of an increase of the number of false negatives by 2. One of those 2 cases was an obvious misinterpretation of the films, in the other case the lesion responsible

for suspicion of malignancy on the screening films was not identical with the carcinoma that appeared subsequently. However, if a positive test is taken as an indication for surgical intervention it may be motivated to avoid 278 unnecessary operations at the price of overlooking 2 carcinomas.

Besides the psychological aspects, a high specificity reduces the need for complementary diagnostic resources and surgical service. In the present project 0.5 % of the participants were operated for benign lesions. Screening about 50 women a day this meant 1.25 "unnecessary" biopsy per week. Breast carcinoma was demonstrated in almost 2 out of 3 women operated upon.

Opinions differ on this aspect of screening. Moskowitz (1979), accepting a yield of only one cancer for every 10 biopsies, has reported that "aggressive" screening with mammography and physical examination significantly increased the detection rate and decreased the rate of interval cases and the rate of advanced disease. Thus, by lowering the diagnostic level of positivity, the sensitivity was increased and the specificity substantially decreased.

The predictive value of a screening test depends not only on the sensitivity and specificity of the screening method(s), but also on the prevalence of carcinoma in the population screened. Most screening programs concern selected groups of women, often selected in an unknown way from an unknown population and hence it is impossible to extrapolate results from such studies to the general female population. In a population-based program a cross-section of the general female population is invited. As the attendance rate is hardly ever 100 %, there is a clear possibility of selectivity also in a population-based series. Without information on non-attenders the representativeness is unknown. In the present project, where the attendance rate was 74 %, the size of carcinomas appearing among non-participants as well as their rate of axillary metastasis and stage of the disease all point to such a selectivity (II). There are large differences in the incidence of breast carcinoma not only between countries

(Cancer Incidence in Five Continents), but also within countries (Cancer Incidence in Sweden 1974, Larsson et al 1978).

In any comparison of the detection rates between various projects the above factors must be considered. The DOM-project (Rombach 1980) and the present project are both population-based with similar attendance rates, 71.5 and 74 %, respectively. Holland as well as Sweden has a high incidence of breast carcinoma (Cancer Incidence in Five Continents). Thus, differences in detection rate would essentially reflect differences in the sensitivity of the detection systems. However, the detection rates were almost identical, 7.6 per thousand in the DOM-project and 7.5 per thousand in the present project.

The efficacy of a screening project could be substantially improved by confining the screening to high-risk groups. However, there seems to be no single risk factor or combination of risk factors, related to breast carcinoma closely enough to make selective screening practicable (Soini 1977, de Waard et al 1978). In other words, in most western countries there seems to be no real low-risk group except young women.

It therefore aroused great interest when Wolfe (1976 a, b) reported that, based on a relatively simple classification of the breast parenchyma at mammography, a high-risk group had been isolated comprising 33 % of the study population who accounted for 82 % of the carcinomas appearing during the period of study. Some later investigators have reached qualitatively similar but quantitatively different results (Peyster et al 1977, Brebner et al 1978, Krook 1978, Krook et al 1978), while others have not been able to reproduce Wolfe's results (Egan & Mosteller 1977, Mendell et al 1977, Rideout & Poon 1977, Fisher et al 1978, Egan & McSweeney 1979). These discrepancies seem to be explained largely by the selection of study populations. The majority of the investigations were case-control studies. Needless to say, it is important that cases as well as controls are representative of all individuals with respectively without the disease or factor studied. For instance, bias may be introduced if cases and con-

trols are not properly age-matched as the distribution of parenchymal patterns varies with age (V). In most studies, the controls emanate from groups of women seeking medical advice for breast complaints. It is quite possible that such women are not representative of the general female population regarding parenchymal patterns.

Thus, it was considered necessary to assess the distribution of the risk factor in question (the parenchymal patterns termed P2 and DY) in the general female population. It cannot be claimed with certainty that the present material (V) is totally representative of the general female population as the study group represented only 71 % of a random sample of the population in the actual ages. However, as discussed above (V), there is reason to believe that the distribution found represents a good estimate of the true distribution. The same applies to the women with carcinoma detected at screening (VI). The results support the fundamental concept of Wolfe, but the relative risk found in the present investigation was substantially lower, 1.5 compared with 9.5 in the first study by Wolfe (1976a). Only 20 % of all breast carcinomas could be attributed to the patterns P2 and DY (VI). Judging from the present results, selective screening of this group is not practicable.

The fact that the P2 and DY patterns were more common in women with breast cancer than in those without in all age-groups studied (VI) together with the variation with age at first delivery (V) indicates that relevant biologic information can be obtained from the appearance of the breast parenchyma in the mammogram.

The proportion of dense tissue as opposed to tissue of fat density (the essential elements of the classification system) might be an expression of the influence of various factors, such as hereditary, hormonal and environmental. In fact, after the completion of the present study (V) data have been published, showing a relation between nulliparity as well as family history of breast cancer and the P2 and DY patterns (Ernster et al

1980). This is clearly a wide field for further research.

The main problem of mammographic screening for breast carcinoma is the impact of the procedure on the mortality of the disease. It might be possible to answer this question within a few years by a comparison between the invited group and the control group regarding the number of deaths due to breast cancer and/or the case fatality rates. In the present investigation an attempt was made to foresee the results by studying known prognostic indicators for breast carcinoma. It should be emphasized that definite conclusions on the basis of such data are not possible. The reason is that the representativeness of the sample of carcinomas obtained at mammographic screening vis à vis symptom-diagnosed series, on which our knowledge of prognostic markers is based, is not known. In the present context the length-bias (as defined in the Introduction) is the most important.

It could be argued that the large proportion of well differentiated tubular carcinomas in the screening sample (II) is an expression of length-biased sampling, as tubular carcinoma is considered to have an exceptionally good prognosis (Cooper et al 1978, Oberman & Fidler 1979) and is therefore probably slow-growing. However, the new dynamic view of tubular carcinoma as representing one stage in the development from a radial scar to an undifferentiated ductal carcinoma (Linell et al 1980) sheds new light on the problem. If the hypothesis of progression is correct, the predominance of well differentiated tubular carcinoma is to be regarded as an expression of early detection of ductal carcinoma. A prerequisite for early finding is the characteristic radiographic appearance of tubular carcinoma, an appearance shared by the radial scar (IV).

The larger proportion of intraductal carcinoma in situ in the screening series than in the clinical series might be an expression of length-biased sampling. Those intraductal carcinomas that produce calcifications can be readily detected by mammography. In general, intraductal carcinoma in situ should be regarded as a precursor of invasive carcinoma (Muir 1941, Gallager & Martin

1969), not only invasive comedocarcinoma, but possibly also medullary carcinoma with lymphoid infiltration and mucoid carcinoma (Linell et al 1980). However, it is quite possible that some radiographically detected intraductal carcinomas in situ would never have become of clinical importance. It is also clear that some comedocarcinomas are not associated with calcifications. This type of carcinoma sometimes forms well delineated tumours difficult to identify in an early stage. Thus, the explanation for the smaller proportion of invasive comedocarcinoma found in the screening series compared with the clinical series might be that some of them were revealed in a non-invasive stage while others that were still small and lacking calcifications were overlooked.

In conclusion, it seems that, although the effect of length-biased sampling is not known, the above results indicate that this factor is of minor or no importance in the group of tubuloductal carcinomas, which constitute about 50 % of all breast carcinomas (Linell et al 1980).

With this reservation in mind it should be emphasized that several significant differences between the screened group and the control group regarding prognostic markers were demonstrated (II), all indicating a more favourable prognosis for the screened group. A comparison with HIP-data would be interesting. However, the HIP-study was focused on a comparison of mortality between the study and control groups and data on, for example, tumour size are incomplete (Shapiro 1977). According to a review of 61 % of the carcinomas, not a single carcinoma smaller than 1 cm was detected by mammography, 2 were detected by physical examination (Thomas et al 1977). Still a more than 30 % reduction of mortality from breast carcinoma was demonstrated in the study group women aged 50 and more, compared with that in their controls (Shapiro 1977). In the present project 43 % (51/118) of carcinomas detected at the first screening were invasive carcinomas with a diameter $\leq$ 10 mm. When carcinomas detected among non-participants and interval carcinomas during the first year after

screening together with carcinomas detected at the second screening were included, the corresponding figure was 39 % (74/190).

In conclusion, mammography was found to be a sensitive and specific method for the purpose of breast cancer screening giving a high yield of "early" carcinomas, i.e. non-invasive carcinoma and invasive with a diameter of at most 10 mm. Although subject to certain bias, such prognostic markers as tumour size, axillary metastasis and stage of the disease indicate a substantial impact of screening on the mortality from breast cancer.

GENERAL SUMMARY AND CONCLUSIONS

A controlled trial to study various aspects of breast cancer screening was described (I). All women, aged 45-69 and living in the city of Malmö were randomly allocated to one of two equally large groups, each consisting of approximately 21,200 women. One group was invited to screening, the other group served as a control group and was not screened. Mammography was the only screening method used. Two projections, craniocaudal and oblique, were used. Seventy-four per cent (15,748) accepted the invitation to the first screening. Carcinoma was demonstrated in 7.5 per thousand (118) of the screenees. Sixteen per cent (19) of the carcinomas were non-invasive and 43 % (51) invasive with a diameter $\leq$ 10 mm. Eighteen per cent (21) had proven axillary metastasis.

Taking interval carcinomas appearing within one year of the screening as a measure of false negatives, the sensitivity of the screening procedure was computed to be 91.5 %. The specificity was 99.2 %.

Of the total number of carcinomas found at the first screening a tumour mass was the main radiographic abnormality in 58 % (68), retraction without obvious tumour mass in 11 % (13) and calcifications in 31 % (36) of the cases (III). The great majority of non-invasive carcinomas, 95 %, were betrayed by calcifications, while 50 % of small invasive carcinomas $\leq$ 10 mm were betrayed by a tumour mass, and 30 % by calcifications.

At retrospective analysis of the screening films 8 % and 6 % of the carcinomas were considered not visible in the craniocaudal and oblique view respectively (III). An additional 3 % were equivocal in each view. With regard to the size of the carcinomas, 16 % of invasive carcinomas $\leq$ 10 mm were considered not visible in the craniocaudal view and 10 % in the oblique view. An additional 4 % were equivocal. Essentially the same results were obtained when also the films taken at the complete mammographic investigation were analyzed. Non-visibility and equivocal find-

ings were most frequent in the youngest age-group, the frequency decreasing with age.

It was concluded that the sensitivity of mammography varies with the number of projections available, as well as with the size of invasive carcinomas and with the age of the patients. It was also concluded that 2 views should be taken, at least at the initial examination.

At screening the mammograms were classified according to Wolfe (1976) as N1, P1, P2 or DY depending on the amount of "prominent ducts" and "dysplasia" in relation to fat. It has been claimed that women with the P2 and DY patterns are at a substantially higher risk of breast cancer than women with the patterns N1 and P1 (Wolfe 1976 a, b).

The influence of age at examination on the parenchymal pattern and the influence of a known risk factor for breast cancer, viz. the woman's age at first delivery, was studied (V). The proportion of mammograms classified as P2 and DY varied with age, decreasing from 66.2 % in the age-group 45-49, to 41.5 % in the age-group 65-69, with a mean of 51 %. Controlling for age at examination, the proportion of mammograms classified as P2 and DY increased with increasing age at first birth and was highest among nulliparae.

Sixty one per cent of the women found to have breast carcinoma at the first screening had either the P2 or the DY pattern (VI). This proportion was significantly different from that of non-cancerous screenees. The relative risk of breast cancer, as estimated from the odds ratio, in women with P2 or DY patterns, compared with women with N1 or P1 patterns varied from 3.1 in the 45-49 year group to 1.3 in the 50-59 year group and was 1.5 for the whole stratum examined.

The overall risk that could be attributed to the P2 and DY patterns was 20 %, varying from 58 % in the 45-49 year group to 13 % in the 50-59 year group.

The results support the fundamental concept of Wolfe, but the relative risk was found to be substantially lower. It was concluded that selective screening of the P2-DY group is not practicable.

Although the definite evaluation of the effect of screening has to be based on a comparison of mortality between the invited and control groups, an attempt was made to produce suggestive information by comparing prognostic markers, such as tumour size and rate of axillary metastasis in the various subgroups of the study population (II). The entire population under study was followed for 1 year. Compared with carcinomas appearing in the control group a significantly larger proportion of small carcinomas (non-invasive and invasive ≤ 10 mm) was found at screening. Furthermore, the proportion with axillary metastasis was significantly smaller as was the proportion with stage I disease. The proportion of non-invasive carcinoma as well as of highly differentiated tubuloductal carcinoma was significantly larger in the screened group than in a control group.

The potential bias inherent in comparisons of the above nature, especially the so-called length-biased sampling was discussed. Interest was focused on the importance of the new dynamic view that tubular carcinoma is an early stage of progression towards less differentiated ductal carcinoma.

A comparison of the radiographic and patho-anatomic appearance of tubuloductal carcinoma was undertaken (IV). Small, highly differentiated tubular carcinoma, like its supposed precursor, the so-called radial scar, was found to be characterized by pronounced retraction of structures surrounding the lesion. With increasing size and decreasing differentiation the tumours tended to be radiographically more clearly circumscribed and the retraction to be less conspicuous. This could be explained by the observation at microscopy that during the progression of tubular carcinoma growth occurred mainly in the fatty tissue between the retracted tissue strands.

Owing to its appearance highly differentiated tubular carcinoma can be readily detected by mammography, which might explain the large proportion of such carcinomas in the present material. This is regarded as an expression of early detection of ductal carcinoma. It was concluded that length-biased sampling is of minor importance in the large group of tubuloductal carcinomas. Hence, it is reasonable to conclude from the above mentioned prognostic markers that screening can be expected to have a substantial effect on the mortality from breast carcinoma.

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From the Departments of Diagnostic Radiology and Preventive
Medicine, University of Lund, Malmö Allmänna Sjukhus,
S-214 01 Malmö, Sweden.

RADIOGRAPHIC SCREENING FOR BREAST CARCINOMA

I. Program and primary findings in 45-69 year old women.

I. Andersson

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Mammary carcinoma is the most common malignant disease in women in Sweden constituting 24 per cent of all cases of carcinoma in women (Cancer Incidence in Sweden 1974). The age standardized incidence rate for the city of Malmö, where the present investigation was performed, was 114.5 per 100 000 women, which was well above the average rate for the whole of Sweden, 85.5 per 100 000.

Long-term follow-up of clinical series of patients with mammary carcinoma has shown that the prognosis varies with the size of the tumour and the state of the axillary lymph nodes at the time of treatment (ADAIR et coll. 1974, SAY & DONEGAN 1974, DUNCAN & KERR 1976, WALLGREN et coll. 1976, ATTIYEH et coll. 1977, FRAZIER et coll. 1977, LANGLANDS & KERR 1978). Early detection of mammary carcinoma by screening should therefore reasonably be followed by reduced morbidity and mortality of the disease. However, survival rates in clinical series are not directly comparable to series detected at screening. The results of a mass examination vary with such factors as lead-time (i.e. the time a tumour would have remained concealed but for the screening, FEINLEIB & ZELEN 1969), length-biased sampling (i.e. the tendency to detect predominantly slow-growing tumours whose prognosis is better than average) and self-selection of the women attending the screening. In one controlled series, the so-called HIP-study, screening of women 50 years of age and older with physical examination supplemented by mammary radiography reduced the mortality by about 30 per cent (SHAPIRO 1977). It is not known to what extent the radiography had contributed to this reduction (BRESLOW et coll. 1977, THOMAS et coll. 1977). No effect was found in women below 50 years of age.

Screening has certain disadvantages (MILLER 1978). For instance it may cause unnecessary anxiety in women falsely suggested of having carcinoma as well as in women in whom carcinoma is demonstrated but who will not benefit from the early detection of the disease. For partly the same reasons some women will be

subjected to unnecessary surgery. The possibility of induction of carcinoma by radiation should be born in mind although the absorbed dose at mammary radiography with modern screen-film systems is very small. The risk has been estimated to be 0.06 cases of breast carcinoma per million women per Gy per year after a latency period of 10 years (BEIR-Report 1972).

The screening should thus be planned in such a way as to enable appraisal of the benefits it offers and of its potential negative effects. This report concerns a cross-sectional randomized screening program and presents basic data from the first screening period.

Material and Methods

The group invited to screening consisted of a 50 per cent random sample of all women in the city of Malmö 45 to 69 years of age. The randomization was done by computer on an individual basis within each year of birth. The remaining 50 per cent acted as a control group which was not screened. Patients from this group with breast complaints attended the ordinary medical service.

The screening was performed between January 1977 and September 1978. Women attending the screening were examined only with mammary radiography using a Philips Diagnost M operated at 28 kV. One craniocaudal and one oblique view were exposed of each breast. For the oblique view the beam was directed about 45° laterally with the woman placed so that the film included the breast and as much as possible of the axilla. Various screen-film combinations were used. Most of the examinations were performed with Kodak Min-R. The films were developed automatically at 31° , in G 137 (Agfa-Gevaert), developing time 57 s, total processing time 4.5 min. The mean absorbed dose was 1 mGy per exposure, as measured with thermoluminescent dosimeter.

The following abnormalities were assumed to indicate carcinoma: (1) A *tumour mass* with an irregular or poorly defined border with or without retraction of tissue strands towards the tumour. Also

a rounded, nodular or lobulated tumour mass, mainly well delineated but poorly defined in some part of the periphery, was considered to indicate carcinoma. Although not decisive the density of a tumour was also taken into account, high density being indicative of malignancy.

(2) Distortion of the normal structure of the breast, usually in the form of *retraction* of the structures in a stellate manner, but without a dominating tumour mass.

(3) Irregular calcifications, i.e. *calcifications* of varying form and size, arranged either disorderly or in a linear fashion, and either appearing in one or more clusters or dispersed in one or more segments of the breast. Obviously benign irregular calcifications, such as those occurring in plasma cell mastitis, fibroadenoma and in the arterial walls, were not included in this group.

Any thickening or retraction of the skin and nipple were also recorded.

If nothing abnormal was detected at the screening no further examination was done. If carcinoma was suggested or if the films did not warrant exclusion of carcinoma, the woman was recalled for complete examination implying in most cases one or more craniocaudal, oblique and lateromedial views and in selected cases also coned-down views. Complete examination was performed within 7 to 10 days of the initial screening examination. If no indication of malignancy was found at the complete examination, the woman was informed without delay and sent home. But if malignancy could not be excluded, the patient was immediately referred for physical examination and fine-needle aspiration biopsy. The findings made with the various methods of examination were discussed at weekly conferences. Surgical biopsy was invariably recommended except in cases where the radiographic findings were very uncertain and physical examination as well as fine-needle aspiration biopsy had revealed nothing abnormal. In these cases the women were kept under observation. If fine-needle aspiration

biopsy, mammary radiography and physical examination had clearly shown carcinoma, mastectomy was carried out without surgical biopsy.

The standard treatment for invasive carcinoma was modified radical mastectomy (MADDEN 1965) and for carcinoma in situ simple mastectomy. Towards the end of the series only wide excisional biopsy was performed in 7 patients with tubular carcinoma < 10 mm across.

Chest films were obtained in all patients to assess the presence of distant metastases. Patients with invasive carcinoma were examined also with skeletal scintigraphy and radiography.

Results

The results are summarized in the Figure. Of the 21 242 women invited, 15 748 accepted. The rate of attendance varied with age, being almost 80 per cent in the lowest age-group and 64 per cent in the highest (Table 1).

Of the women screened 3.4 per cent were referred for complete examination, which confirmed abnormalities suggestive of malignancy in approximately half of them (Table 2). In the other half, tumour had in most cases been suggested due to superimposition of normal structures simulating an irregular mass. In 1.6 per cent of the women the mammary radiography showed either clear or suggestive signs of carcinoma. These women were the only ones that were referred for further examination. Except for the age group 55 to 59, neither the rate of suggestive findings at screening nor at complete radiography varied significantly with age.

The subsequent results of the 250 women in whom carcinoma had been suggested at the complete examination are summarized in Table 3.

Fig. Schematic representation of the project

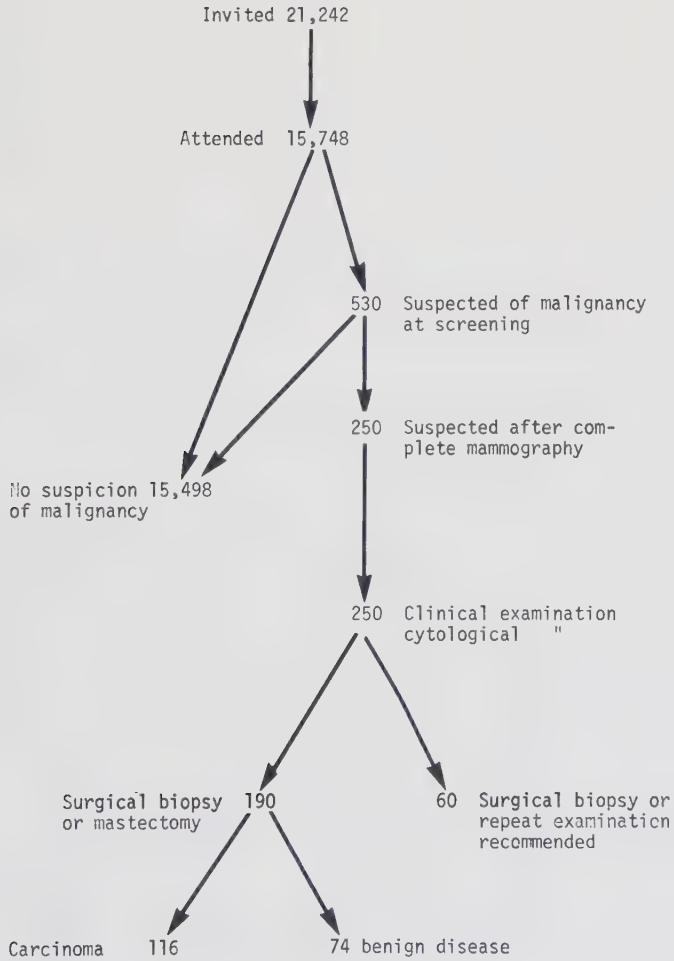


Table 1. Number of women invited and rate of attendance by age

Age	No. invited	Attending after				Total attending	
		First invitation		Second invitation			
		No.	Per cent	No.	Per cent	No.	Per cent
45-49	3 795	2 530	66.7	453	11.9	2 983	78.6
50-54	4 321	3 074	71.1	381	8.8	3 455	79.9
55-59	4 617	3 072	66.5	458	9.9	3 530	76.4
60-64	4 324	2 782	64.3	321	7.4	3 103	71.7
65-69	4 185	2 377	56.8	300	7.2	2 677	64.0
45-69	21 242	13 835	65.1	1 913	9.0	15 748	74.1

Table 2. Number of women suspected of carcinoma at screening and after complete examination.

Age	No. examined	Suspect at screening		Suspect after complete examination	
		No.	Per cent	No.	Per cent
45-49	2 983	125	4.2	39	1.3
50-54	3 455	111	3.2	63	1.8
55-59	3 530	88	2.5	48	1.4
60-64	3 103	100	3.2	49	1.6
65-69	2 677	106	4.0	51	1.9
45-69	15 748	530	3.4	250	1.6

Table 3. Results in 250 women selected at screening

	No.	Per cent
Carcinoma	118	47.2
Benign biopsy	74	29.6
Biopsy recommended	3	1.2
Considered benign at follow-up	49	19.6
Not attending follow-up	5	2.0
Dead	1	0.4
TOTAL	250	100

Table 4 shows that 190 women were operated upon, i.e. 1.2 per cent of those screened and 76 per cent of those in whom carcinoma had been suggested at complete radiography, 165 being operated upon because of findings made at the initial examination and 25 after a follow-up of 1.5 to 23 months (median 9 months).

Table 4. Number of women operated upon with respectively carcinoma or benign breast disease by age. Figures within brackets denote rate per thousand within each age group

Age	No. of women operated		No. of women with carcinoma		No. of women with benign biopsy	
45-49	26	(8.7)	14 [*]	(4.7)	12	(4.0)
50-54	47	(13.6)	23 ^{**}	(6.7)	24	(6.9)
55-59	38	(10.8)	21	(6.0)	17	(4.8)
60-64	42	(13.5)	28	(9.0)	14	(4.5)
65-69	37	(13.8)	30	(11.2)	7 ^{***}	(2.6)
45-69	190	(12.1)	116	(7.4)	74	(4.7)

* Two patients operated upon after follow-up

** One patient operated upon after follow-up

*** One woman subjected to bilateral biopsy

Carcinoma was confirmed in 116 (61 %) of the women operated upon, of these 3 patients with carcinoma were operated upon after a follow-up of 3 months (medullary carcinoma, diameter 1.5 cm), 10 months (tubular carcinoma < 1 cm) and 17 months (intraductal carcinoma in situ), respectively. A further 2 women, in whom a tumour mass characteristic of carcinoma, was found at mammary radiography and clearly confirmed by fine needle aspiration biopsy, refused operation. Thus, all together 118 women had carcinoma.

In 5 patients with carcinoma a biopsy specimen was obtained also of the contralateral breast. In one of these specimens a lobular carcinoma in situ was revealed. Radiography had not shown anything abnormal and biopsy was made because of an extensive lobular carcinoma in situ together with invasive lobular carcinoma in the primarily operated breast. The biopsy specimens of the remaining 4 were benign. Two patients had been treated for contralateral breast carcinoma, 12 and 14 years previously.

The diagnoses of the benign lesions in biopsy specimens are given in Table 5. Nine per cent of the specimens showed epithelial proliferations with atypia and 12 per cent radial scars (LINELL et coll. 1980).

The patients operated upon because of benign lesions constituted 46 to 51 per cent of the total number of women operated upon in the lowest age groups, decreasing successively to 19 per cent in the highest age group, with a mean of 39 per cent.

The carcinoma detection rate by age appears in Table 6. The material was divided into 3 groups, (1) carcinoma in situ, (2) invasive carcinoma 10 mm or less in diameter, and (3) invasive carcinoma more than 10 mm in diameter. The tumours were measured on the unfixed specimens except those in 5 cases, which were measured on the films. The largest of two diameters was recorded. In the presence of multiple tumours the size of the largest tumour was recorded.

Table 5. Diagnoses on basis of biopsies from 74 women

	Number	Per cent
Epithelial proliferation with atypia	7	9
Epithelial proliferation without atypia	9	12
Radial scars	9	12
Cystic mastopathy	38	51
Sclerosing adenosis	24	32
Fibroadenoma	12	16
Duct ectasia	8	11
Miscellaneous	8	11

Table 6. Detection rate of breast carcinoma by age. Figures within brackets denote rate per thousand within each age group

	Carcinoma in situ	Invasive carcinoma		Total
		≤ 10 mm	> 10 mm	
45-49	2 (0.7)	7 (2.3)	5 (1.7)	14 (4.7)
50-54	4 (1.2)	10 (2.9)	9 (2.6)	23 (6.7)
55-59	2 (0.6)	8 (2.3)	11 (3.1)	21 (6.0)
60-64	3 (1.0)**	14 (4.5)	12 (3.9)***	29 (9.3)
65-69	8 (3.0)	12 (4.5)*	11 (4.1)	31 (11.6)
45-69	19 (1.2)	51 (3.2)	48 (3.0)	118 (7.5)

* Diagnosis based on radiography and cytology in one patient in respective group.

** One patient treated for invasive carcinoma of the contralateral breast 12 years previously: no metastasis

*** One patient treated for carcinoma of the contralateral breast 14 years previously: no metastasis.

It is evident that the detection rate increased from 4.7 per thousand in the youngest quinquennium to 11.6 in the oldest, with a mean of 7.5. However, the increase was not continuous, the prevalence rate in the 55-59-year group being lower than in the 50-54-year group. Fifty-nine per cent of the carcinomas were either carcinoma in situ or invasive carcinoma ≤ 10 mm.

More detailed information on the sizes of the malignant lesions is found in Table 7.

Table 8 gives the frequency of axillary metastases at the time of operation. Assuming that patients who had not been subjected to axillary exeresis had no metastases, it would mean that in 96 per cent of the patients with either carcinoma in situ or invasive carcinoma 10 mm or less, the disease had not spread to the axilla. The corresponding figure for invasive carcinoma > 10 mm was 62 per cent. No distant metastasis was demonstrated in any of the patients.

Within the first year of screening malignant lesions were detected in 11 of the women screened (10 carcinomas and 1 sarcoma). In two of these women tumours had been suspected at screening but ruled out at complete radiography. Accepting the appear-

Table 7. Carcinomas by size and age of the patients. Figures within brackets denote per cent.

	Age group						
	45-49	50-54	55-59	60-64	65-69	70-74	
Carcinoma in situ	2	4	2	3	8	19	(16)
≤ 10 mm	7	10	8	14	12	51	(43)
11-20 mm	5	8	8	11	7	39	(33)
21-50 mm		1	2	1	3	7	(6)
> 50 mm			1		1	2	(2)
Total	14	23	21	29	31	118	(100)

Table 8. Axillary metastases by size of the primary tumour

	Total no. of patients		Patients with axillary metastases			Total with axillary metastases	
			No. of nodes involved		With penetration of node capsule		
			1-3	4-			
Carcinoma in situ	19	(13)*				0	
≤ 10 mm	51	(8)	2	1	3	3	6
11-20 mm	39	(1)	8	4	6	12	36
21-50 mm	7		2	2	2	4	57
> 50 mm	2			2	2	2	100
	118	(22)	12	9	13	21	18

* exeresis not performed

ance of a malignant tumour within one year as a measure of false negatives, the sensitivity, specificity and predictive value, calculated according to GALEN & GAMBINO (1975) were as follows (Table 9):

The sensitivity of the screening procedure: 91.5 per cent [(TP / TP + FN) x 100].

The specificity of the screening procedure: 97.4 per cent [(TN / TN + FP) x 100].

The specificity of the screening procedure plus complete radiography: 99.2 per cent.

The predictive value of a positive (suspected) finding at screening 22.3 per cent [(TP / TP + FP) x 100].

The predictive value of a positive finding at complete radiography: 47.2 per cent.

The predictive value of a negative (not suspected) finding: 99.9 per cent [(TN / TN + FN) x 100].

Table 9. Data for calculating sensitivity, specificity and predictive value. TP = true positives, i.e. number of women with breast carcinoma, correctly classified at radiography. FN = false negatives, i.e. number of women with breast carcinoma, misclassified at radiography. TN = true negatives, i.e. number of healthy women, correctly classified at radiography. FP = false positives, i.e. number of healthy women, misclassified at radiography.

	With positive radiography	With negative radiography	Total
With breast carcinoma	118 (TP)	11 (FN)	129
Without breast carcinoma	412 (FP) (132)*	15 207 (TN) (15 487)*	15 619
			15 748

* After complete radiography.

Discussion

The only well-documented method for detecting preclinical breast carcinoma is mammary radiography (LÁNYI & LITTMANN 1970, EGAN 1971, WOLFE 1974, HERMANUTZ et coll. 1974, MALONE et coll. 1975, MENGES et coll. 1976, FRISCHBIER & LOHBECK 1977, BJURSTAM 1978). Furthermore, this examination can demonstrate 90 to 98 per cent of all clinically suspected carcinomas (BJURSTAM et coll. 1974, WOLFE 1974, FRISCHBIER & LOHBECK).

Therefore, it seems reasonable to use mammary radiography alone in screening projects, particularly since the feasibility of this principle has been demonstrated by LUNDGREN (1979 a, b) who introduced breast carcinoma screening with single-view radiography (LUNDGREN & JAKOBSSON 1976). Almost all other projects on

record have included physical examination, some of them also thermography (GERSHON-COHEN et coll. 1961, WITTEN & THURBER 1964, WOLFE 1965, DOWDY et coll. 1971, VENET et coll. 1971, STARK & WAY 1974, CHAMBERLAIN et coll. 1975, GEORGE et coll. 1976, STRAX 1976, FEIG et coll. 1977, EDINBURGH Breast Screening Clinic 1978, BEAHRS et coll. 1979).

It is not possible to decide to what extent supplementary physical examination would have increased the number of tumours diagnosed in the present series. Previous reports give widely varying results. In the Breast Cancer Detection Demonstration Projects (BCDDP) 7 to 8 per cent of the carcinomas were detected by physical examination alone (BEAHRS et coll.). However, the figures in the separate projects varied widely, viz. from 0 to 23.8 per cent. In 13 of the 29 projects no malignant lesions at all were detected by physical examination alone. At the first screening of the BCDDP physical examination alone revealed 9 per cent of so-called minimal carcinoma (carcinoma in situ and invasive carcinoma < 1 cm) and at the second screening 3.7 per cent.

FEIG et coll. and CHAMBERLAIN et coll. investigated the independent contribution by radiography and physical examination at screening for breast carcinoma. They found that 22 and 19 per cent, respectively, of the carcinomas were detected by physical examination alone.

LANGELAND (1970) investigated the value of physical examination alone at screening. The investigation was performed in the same city as the present one, although 10 years earlier. At initial screening the detection rate was 2.1 per 1 000 in the ages between 40 and 67. Most of the tumours were large, the smallest measuring 2 cm x 1 (by palpation). All the tumours were invasive and 6 (49%) of 13 had given axillary metastases. Due to the small number of cases it could not be decided whether the proportion of carcinoma stage I was larger in the screened group than in the non-screened part of the population in the corresponding ages. No statistically significant difference was found between the carci-

noma prevalence in the screened group and the incidence in the non-screened group.

Various explanations may be offered for the large differences between the reported value of physical examination. The most readily available explanation seems to be a variation in the quality of the films and the skill of the radiologist examining them. High-quality films examined by an experienced radiologist would leave fewer carcinomas to be detected by physical examination alone compared with a situation with low-quality films and a radiologist with less experience. Also other factors such as the skill of the clinical physician, and the composition of the patient material are of importance.

The inclusion of physical examination in a screening project obviously implies a substantial increase in the rate of false positive findings, i.e. a reduction of its specificity. CHAMBERLAIN et coll. found the biopsy rate for non-malignant conditions to be 7 per cent for physical examination. In the series of LANGE LAND the rate of benign biopsies was 3.1 per cent at the first screening and 3.6 at the second. False positive results imply apparent disadvantages of not only psychologic but also of physical nature due to a certain risk of morbidity following surgery and anaesthesia.

In order to reduce overdiagnosis, all women with suspect carcinoma at the screening were recalled for complete radiographic examination. This reduced the number of false positive cases by almost 70 per cent. The biopsy rate for benign conditions was 0.5 per cent, in other series the corresponding rate has varied between 1.7 and 8.4 per cent (DOWDY et coll., CHAMBERLAIN et coll., LEWIS et coll. 1975, STRAX, MOSKOWITZ et coll. 1976, FEIG et coll., GEORGE et coll., SAYLER et coll. 1977, Edinburgh Breast Screening Clinic) with the exception of the series of LUNDGREN who reported 0.2 to 0.3 per cent (LUNDGREN & JAKOBSSON, LUNDGREN 1979 b).

As pointed out by GALEN & GAMBINO, the predictive value of a positive test varies with the prevalence of the disease in the population. It appears from the results that even with a sensitivity of 91 per cent and a specificity of 99 per cent, the predictive value of a positive mammary radiography was only 47 per cent. This is explained by the fact that breast carcinoma is a relatively rare disease, with a prevalence of less than one per cent in the ages in question. With a specificity of 90 per cent, other factors being constant, the predictive value of a positive test would have been only 7 per cent. This underlines the necessity of a high sensitivity and specificity of a screening test in a population with a low prevalence of the disease in question. The sensitivity, specificity and predictive value of the present series are in close agreement with those reported by de WAARD et coll (1978).

The problem of the radiation hazards of mammary radiography has received considerable attention (BAILAR 1976, 1977). It has been shown beyond doubt that roentgen radiation can induce breast carcinoma. This knowledge is based on an excessive rate of breast carcinoma in patients exposed to comparatively large doses (more than an average of 1 Gy in most series) at chest fluoroscopy (MacKENZIE 1965, MYRDEN & HILTZ 1969, GRUNDY & UZMAN 1973, COOK et coll. 1974, BOICE & MONSON 1977) or in the treatment of post-partum mastitis, fibroadenosis or other benign conditions (METTLER et coll. 1969, SHORE et coll. 1977, BARAL et coll. 1977) and in the survivors of the atomic bombings of Hiroshima and Nagasaki (WANEBO et coll. 1968, McGREGOR et coll. 1977, TOKUNAGA et coll. 1979). Whether a linear dose-risk relationship exists down to the very low doses at modern mammary radiography is still an open question. However, there is considerable evidence that the carcinogenic effect of radiation is age-dependent, with a higher risk at low ages. On the basis of the material of BARAL et coll., the doubling dose (i.e. the dose which doubles the incidence of breast carcinoma was calculated to be 1.5 Gy in the age group 30 to 34 and 4.9 Gy in the age group 40 to 44 (age at irradiation). An expert committee appointed by the U.S. National

Cancer Institute to review the state of knowledge of the radiation risk of screening with mammary radiography (UPTON et coll. 1977) calculated it to be approximately between 3.5 and 7.5 cases of breast carcinoma per million women 35 years of age or older at risk per year per 0,01 Gy to both breasts from the tenth year after irradiation throughout life. This would mean that 0.1 or 0.2 carcinomas was induced by the radiographic examinations in the present screening, assuming that the participants had a mean life expectancy of 20 years.

There is no general agreement as to which age groups should be screened. Factors such as detection rate, radiation dose, and life expectancy of the women to be screened have to be considered.

In the present series the detection rate was 4.7 per 1 000 in the 45 to 49-year age group. The proportion of small carcinomas and the proportion of patients without axillary metastases was approximately the same for this age group as for the older age groups. In the BCDDP the detection rate was 5.87 per 1 000 in the age group 45 to 49, 3.12 per 1 000 and 1.50 per 1 000 in the age groups 40 to 44 and 35 to 39 respectively. However, this program was not cross-sectional. LUNDGREN (1979 a) found carcinoma in only one of 1 489 women, aged 35 to 39 and has abandoned screening women below 40 years of age.

Although data showing a benefit of screening women under the age of 50 have hitherto been lacking, the data mentioned indicate that it is worthwhile and that screening should be started somewhere around 40 to 45 years of age.

Some programs have set an upper age limit, e.g. 74 years in the BCDDP and 59 years in the Edinburgh Breast Screening Clinic, while others have not (DOWDY et coll., CHAMBERLAIN et coll., GEORGE et coll., LUNDGREN & JAKOBSSON, LUNDGREN 1979 b).

In order to decide what upper age limit is feasible, data on women who had their carcinoma diagnosed at the age of 70 or later

were obtained from the files of the Clinic of Oncology^{*}, Malmö Allmänna Sjukhus; 115 such cases diagnosed 1960 to 1964 were traced. After a minimum follow-up of 14 years, 52 per cent had died from other diseases, 39 per cent from breast carcinoma, and 9 per cent were alive without metastases. For those who were 75 years or more at diagnosis, the corresponding figures were 60 per cent from intercurrent diseases, 37 per cent from breast carcinoma and 3 per cent alive. The autopsy-rate was 76 per cent. Thus, although the majority of patients 70 years or age or older at diagnosis died from intercurrent diseases, a considerable proportion had died of their breast carcinoma. It was shown by MUELLER et coll. (1978) that the death rate, i.e. the rate at which breast carcinoma expresses its lethality was higher in older than in younger age groups. The difference could not be explained by over-representation of more advanced stages in older age. It might therefore be advisable to continue screening for some years past 70.

The rate of attendance was 74 per cent, which is about the same as in LANGE LAND's material. LUNDGREN (1979 b), whose material emanated from rural areas and small towns, reported a rate of attendance over 90 per cent in the actual age groups. In a cross-sectional screening project of the population of the city of Utrecht, the attendance rate was reported to be 71.5 per cent in the 50 to 64 year group (de WAARD et coll). The attendance rate thus appears to depend on whether the population is urban or rural and whether an urban population is small or large.

In the present project the reasons for non-participation was not systematically analysed. However, women attending the second but not the first screening were asked why they did not attend the first screening. This group is probably not representative of the entire group of non-responders. Of 100 randomly selected women, 29 said that they had recently undergone mammary radiography or physical examination of the breast, 24 that they were away from home at the time, and 14 that they were ill. The re-

* Head: Inge Gynning, whose help is gratefully acknowledged.

maining 33 women gave 17 various reasons for not participating. It should be pointed out that approximately one month had elapsed between the first and second invitation.

When comparing detection rates of carcinoma in different screening programs, it should be borne in mind that the detection rate is influenced by several factors besides the sensitivity of the screening procedure, such as the method of patient selection, and the natural incidence rate. Also, the histologic criteria for malignancy vary (BEAHRS et coll., BEAHRS & SMART 1979).

With these reservations in mind it may be mentioned that the detection rate on initial screening in the HIP-study was 2.72 per 1 000 (40-64-year group; SHAPIRO et coll. 1971) and in the BCDDP 6.7 per 1 000 in the 45 to 64-year group (BEAHRS et coll.). The HIP-study was started in 1962 and the BCDDP in 1973 and the difference probably reflects the progress of the radiographic technique. In the present series the detection rate was 7.5 per 1 000. The same detection rate was reported by de WAARD et coll. in the 50-64-year group. In cross-sectional screening projects in other regions of this country with lower incidence rates than Malmö, the detection rate varied between 3.2 and 7.0 per 1 000 in the ages 40 to 69 (LUNDGREN & JAKOBSSON, JAKOBSSON & LUNDGREN 1976, FAGERBERG 1980, TABÁR & GAD 1980).

More relevant is probably the proportion of small carcinomas and carcinomas without axillary metastases. In the BCDDP (BEAHRS et coll.) 38 per cent were either carcinoma in situ or invasive < 10 mm. For cases detected at radiography alone the corresponding figure was 48 per cent. LUNDGREN (1979 b) reported 54 per cent to be either carcinoma in situ or invasive $\leq$ 10 mm, TABÁR & GAD 44 per cent and FAGERBERG 52 per cent. In the present material the corresponding figure was 59 per cent.

In the HIP-study 70 per cent of the carcinomas detected at screening were reported free of axillary metastases (SHAPIRO et coll.), in the BCDDP 63 per cent, while nothing was known in a further 19 per cent (BEAHRS et coll.). Thus, at most 82 per cent

were free from axillary metastases in the BCDDP. FEIG et coll. reported 71 per cent, CHAMBERLAIN et coll. 71 per cent (15/21), and Edinburgh Breast Screening Clinic 67 per cent (12/18) to be free from axillary metastases. The highest figure, 91 per cent, was reported by LUNDGREN (1979 b). However, it should, be observed that the majority of the axillae were not explored surgically; in the present series 22 were not explored. Thirteen of these were carcinoma in situ and another 7 were invasive tubular carcinoma measuring only a few millimeters. If these 22 axillae are considered negative, 82 per cent of the present patients were free from axillary metastases which compares well with the results of the BCDDP.

It is concluded that screening with mammary radiography is an effective method for detecting early carcinoma, defined here as non-invasive carcinoma and invasive carcinoma at most 10 mm in diameter. Although it has to be assessed by a long-term follow-up, there is good reason to believe that screening will reduce breast carcinoma mortality.

Summary

A cross-sectional, randomized screening with mammary radiography of 15 748 women aged 45 to 69 and living in Malmö for the detection of breast carcinoma is described. The detection rate of breast carcinoma was 7.5 per 1 000, 16 per cent of the carcinomas being non-invasive and 43 invasive with a diameter of at most 10 mm. The overall rate of axillary metastases was 18 per cent. The sensitivity of the radiography was 91.5 per cent, the specificity 99.2 per cent and the predictive value 47 per cent. It is concluded that mammary radiography is an effective screening method for detecting early carcinoma.

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FROM THE DEPARTMENTS OF DIAGNOSTIC RADIOLOGY AND PREVENTIVE
MEDICINE, UNIVERSITY OF LUND, MALMÖ ALLMÄNNA SJUKHUS,
S-214 01 MALMÖ, SWEDEN.

RADIOGRAPHIC SCREENING FOR BREAST CARCINOMA

II. Prognostic considerations on the basis of a short-term follow-up.

I. Andersson

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The main purpose of screening for breast carcinoma is to reduce the mortality as well as the morbidity of the disease. In the so-called HIP-study such screening reduced the mortality from breast carcinoma in women 50 years of age or more and having an annual check-up with physical examination and mammary radiography (SHAPIRO 1977, 1978). In younger women no such effect was found. It is not clear to what extent radiography had contributed to the reduction. Furthermore, the diagnostic capacity of mammary radiography has since been improved. For these reasons a controlled, prospective trial to demonstrate the effect of radiographic screening on the mortality and morbidity seemed to be justified and was started in the city of Malmö in January 1977.

Analysis of the effect of screening on mortality must abide further follow-up. In the meantime the results of comparisons between the invited group and the control group concerning prognostic factors, such as tumour size, rate of axillary metastases and stage of the disease, might be suggestive. The present report also included the distribution of microscopic types of carcinoma in the screened group and in a control group.

Material and Methods

All women aged 45 to 69 years (birth cohorts 1908 - 1932) and living in the city of Malmö were randomly assigned to one or the other of two groups. Each group consisted of approximately 21 200 women. One group was invited to screening, the other was not and served as controls. Mammary radiography was the only screening method used. More detailed information on the screening project is given in Part I (ANDERSSON).

The first screening was performed between January 1977 and September 1978. All the women who belonged to the birth cohorts 1908 to 1932 and in whom breast carcinoma was diagnosed within one year of the date of entry into the screening project were

recorded. It was also noted whether such a patient had participated in the screening project or had declined the invitation to participate or belonged to the control group.

The standard surgical treatment for invasive carcinoma was modified radical mastectomy, i.e., mastectomy with preservation of the pectoral muscles and exeresis of the axillary content en bloc. The standard treatment for non-invasive carcinoma was either simple mastectomy or subcutaneous mastectomy. Towards the end of the period some patients with stage I tumours were treated with local excision of the tumour, followed by irradiation of the breast.

The tumours were measured by the pathologists in unfixed specimens or, when not possible, on the films (6 cases). The longest diameter was noted. Methods used in the pathologic examination, including the microscopic classification, are described elsewhere (LINELL et coll. 1980). In order to avoid inter-observer variation, the microscopic classification was done by one observer. The material of LINELL et coll. was used for the analysis of the distribution of the microscopic types of carcinoma. The clinical series which was used for comparison with the screening series consisted of consecutive patients in the birth cohorts 1908 to 1932 and examined during 1976 to 1978. With few exceptions these patients had been referred for diagnostic evaluation of breast complaints.

The stage of the disease was assessed according to the TNM-classification (UICC 1978). The T (tumour) and N (nodal) category was determined from the pathologist's report except the T-category of the mentioned patients whose tumours were measured on the films. Furthermore, clinical staging was done in 7 inoperable patients. In a few patients with non-invasive or small invasive carcinomas, and who had not been subjected to axillary exeresis, the nodal status was assessed by palpation (all negative). Patients with invasive carcinoma were referred for radiographic examination of the chest and skeleton and bone scintigraphy for metastases; patients with non-invasive carcinoma, only for chest radiography.

The data on re-screening presented in the following refer to a random sample of about 55 per cent ($n = 11\ 528$) of those invited to the first screening. The radiographic technique used at the second examination differed from that at the first in two respects, viz. another film was used (Kodak NMB), and the kV-setting was reduced from 28 to 25.

Unless otherwise stated, statistical comparisons were made with Chi-square test.

Results

The first screening revealed carcinoma in 118 women corresponding to a detection rate of 7.5 per thousand.

During the 1-year follow-up breast carcinoma was diagnosed in 11 (0.7 per thousand) women, who had participated in the screening (interval carcinomas), in 18 (3.3 per thousand) women who had been invited but not participated and in 51 (2.4 per thousand) women belonging to the control group.

Of the 51 carcinomas detected in the control group 4 were not palpable and in another 5 the clinical findings were inconclusive. In the group of non-participants one carcinoma was not palpable. The same applied to 3 interval carcinomas. The patients with non-palpable tumours sought advice for symptoms apparently unrelated to the malignant tumours. These tumours were demonstrated at radiography.

At retrospective analysis of the screening films 3 of the interval carcinomas were considered diagnostic failures. Another 3 could be seen retrospectively but the abnormalities were not characteristic enough to suggest carcinoma. In the remaining 5 cases no abnormalities could be seen retrospectively.

Two patients in the control group had synchronous bilateral carcinoma and another 3 had been treated 28, 17 and 11 years previously for contralateral breast carcinoma without evidence of

a recurrence. Two patients in the group of non-participants had synchronous bilateral carcinoma and another 2 had been treated 4 and 2 years previously for contralateral carcinoma without any evidence of a recurrence. Of the women found to have carcinoma at screening, the condition was bilateral synchronous in one, and 2 had been treated 12 and 14 years previously for carcinoma in the contralateral breast without any evidence of a recurrence.

The age-distribution and the age-specific carcinoma rates in the various subgroups are given in Table 1. The detection rate at screening, 7.5 per thousand, was significantly higher than the incidence rate in the control group, 2.4 per thousand ($p < 0.005$). The incidence rate in the screened group during the first year after screening, 0.7 per thousand, was significantly lower than the incidence rate in the control group ($p < 0.005$). The incidence in the group of non-participants was higher, though not significantly, than in the control group.

Table 1. Age distribution and age specific rates per thousand (within brackets) of women with breast carcinoma by group. Population as defined at the start of the screening. In the calculation of the age specific incidence rates the population was corrected for deaths and migration.

	Age group					
	45-49	50-54	55-59	60-64	65-69	45-69
Control group (n = 21 240)	7 (1.8)	8 (1.9)	12 (2.6)	8 (1.9)	16 (3.8)	51 (2.4)*
Screened group (n = 15 748), carcinomas detected at screening	14 (4.7)	23 (6.7)	21 (6.0)	29 (9.3)	31 (11.6)	118 (7.5)*
Non-participants (n = 5 494)	0	4 (4.6)	2 (1.8)	5 (4.1)	7 (4.6)	18 (3.3)
Screened group, interval carcinomas	3 (1.0)	2 (0.6)	2 (0.6)	2 (0.6)	2 (0.7)	11 (0.7)*

* p-value for observed differences between screened group and control group < 0.005 .

It is evident from Table 2 that the proportion of non-invasive and invasive carcinoma with a diameter of at most 10 mm was substantially larger among carcinomas found at screening than in the control group, 59 and 16 per cent, respectively ($p < 0.005$). The proportion of large carcinomas (> 50 mm) was higher among the

non-participants than among the controls, 22 and 2 per cent, respectively ($p < 0.005$). The size of the interval carcinomas did not differ significantly from those in the control group.

Table 2. Tumour size by group. If bilateral, the largest tumour was recorded. Figures within brackets denote percentages.

	Invasive carcinoma				Not defined	Carcinoma in situ	Total	Median size (mm), invasive carcinoma
	≤ 10 mm	11-20	21-50	> 50				
Control group	8 (16)**	18 (35)	22 (43)	1 (2)	2 (4)	0	51 (100)	20
Screened group, carcinomas detected at screening	51 (43)**	39 (33)	7 (6)	2 (2)		19 (16)**	118 (100)	8
Non-participants	1 (5)	7 (39)	5 (28)	4 (22)***	1 (6)	0	18 (100)	25
Screened group, interval carcinomas	2 (18)	6 (55)	2*(18)			1 (9)	11 (100)	17

* 1 Fibrosarcoma

** p-value for observed difference between screened group and control group < 0.005

*** p-value for observed difference between non-participants and control group < 0.005

The rate of axillary metastasis (Table 3) was significantly lower among women in whom carcinoma had been detected at screening than among their controls ($p < 0.005$). The rate of axillary metastasis among non-participants was higher, but did not differ significantly from that in the controls ($p > 0.05$); neither did the interval cases. Among patients with metastases, the proportion

Table 3. Axillary metastases by group. Patients with carcinoma in situ have been excluded from the table

	Total No. of patients	Patients with axillary metastases			Total with axillary metastases	
		No. of nodes involved		With penetr of node capsule	No.	Per cent
		1 - 3	4 -			
Control group	51 (3)*	14	10	14	24	47**
Screened group, carcinomas detected at screening	99 (9)*	12	9	12	21	21**
Non-participants	18 (5)*	2	3	3	10****	56***
Screened group, interval carcinomas	9	2	1	3	3	

* Axillary exeresis not performed.

** p-value for observed difference between screened group and control group < 0.005 .

*** p-value for observed difference between non-participants and control group > 0.05 .

**** Assessed by palpation in 5 patients, all with advanced disease.

with at most 3 nodes affected was similar in the screened group and the control group as was the proportion with penetration of the node capsule. The median size of carcinomas with axillary metastasis in the screening group was 16 mm. The corresponding figure for the control group was 23 mm.

The proportion of disease stage I was significantly higher in the screened group, 76 per cent, than in the control group, 29 per cent ($p < 0.005$, Table 4). Even if interval carcinomas and carcinomas among non-participants be added to the group found at screening, the difference will still be highly significant. The proportion of stage III and IV was significantly higher in non-participants than in the other groups ($p < 0.005$).

Table 4. Stage distribution by group. Patients with carcinoma in situ have been excluded. Figures within brackets denote percentages.

	Stage				Not classifiable	Total
	I	II	III	IV		
Control group	15 (29)*	27 (53)	6 (12)	1 (2)	2 (4)	51 (100)
Screened group, carcinomas detected at screening	75 (76)*	22 (22)	2 (2)			99 (100)
Non-participants	6 (33)	3 (17)	5 (28)**	4 (22)**		18 (100)
Screened group, inter- val carcinomas	6	2	1			9

* p-value for the observed difference between screened group and control group < 0.005

** p-value for the observed difference between non-participants (combined stage III and IV) and the other groups < 0.005 .

The tumour size and rate of axillary metastasis among carcinomas found at the first and second screening are compared in Table 5. An even larger proportion of small carcinomas (non-invasive and invasive ≤ 10 mm) was found at the second than at the first screening, 70 and 59 per cent, respectively. Due to the small numbers the difference was not statistically significant. The total rate of axillary metastases was approximately the same.

However, the proportion of small invasive carcinomas with metastases was larger at the second than at the first screening, 20 and 6 per cent, respectively. The difference is not statistically significant.

Table 5. Per cent distribution of carcinomas found at the first (n = 118) and second (n = 43) screening by size. Figures within brackets denote per cent of patients with axillary metastases.

	Carcinoma in situ	≤ 10 mm	11 - 20	21 - 50	> 50	Total
First screening	16 (0)	43 (6)	33 (36)	6 (57)	2 (100)	100 (18)
Second screening	23 (0)	47 (20)	19 (25)	12 (60)		100 (21)

The microscopic classification of the carcinomas found at the first screening is compared with carcinomas in a clinical series in Table 6 (LINELL et coll.). In the clinical series 92 per cent of the carcinomas were classified as invasive compared with 84 per cent in the screened series ($p < 0.025$). Tubuloductal carcinomas were more frequent in the screening series than in the clinical series ($p < 0.05$). Furthermore, the proportion of highly differentiated tubular carcinoma (++++ and +++) was 60 per cent in the screening series compared with 30 per cent in the clinical series ($p < 0.001$). Like the rate of axillary metastases the size of the malignant growths generally increased with decreasing degree of differentiation (tubular carcinoma ++++ $\rightarrow$ 0, LINELL et coll.).

The proportion of intraductal carcinoma in situ was larger in the screening series, while the proportion of invasive carcinoma of 'comedo' type as well as mucinous carcinoma and medullary carcinoma with lymphoid infiltration was larger in the clinical series.

Table 6. Carcinomas by microscopic type. The carcinomas were classified according to LINELL et coll. (1980).

	Screening series		Clinical series	
	No.	Per cent	No.	Per cent
INVASIVE CARCINOMA				
A. Tubuloductal carcinoma				
1. Pure tubular (++++)	25	21.5	16	6.7
2. Preponderantly tubular, admixture of less differentiated ductal structures (+++)	16	13.8	19	8.0
3. Large proportion of tubules but predominantly ductal structures (++)	13	11.2	21	8.8
4. Only few tubules (+)	11	9.5	31	13.0
5. No tubules, otherwise same as No. 4 (0)	3	2.6	28	11.8
Tubuloductal total	68*	58.6	115	48.3
B. Ductal carcinoma of comedo type	15	12.9**	58	24.4
C. Lobular carcinoma	12	10.3	26	10.9
D. Medullary carcinoma with lymphoid infiltration	1	0.9**	17	7.1
E. Mucinous (colloid) carcinoma	1	0.9	4	1.7
NON-INVASIVE CARCINOMA				
A. Intraductal carcinoma in situ including Paget's nipple disease	16	13.8	11	4.6
B. Lobular carcinoma in situ	3	2.6	7	3.0
TOTAL	116	100.0	238	100.0

* p-value for observed difference between screening and clinical series < 0.05.

** p < 0.001 (standard binomial test).

Discussion

Prognostic markers, such as tumour size and stage of the disease, which have been established in clinical series are not directly applicable to a screened series. This is due to certain factors operating in association with screening (FEINLEIB & ZELEN, 1969). First, the time of diagnosis is advanced through screening, which will bias a comparison of survival unless the length of this period (lead-time) can be estimated. The second factor is the tendency of screening to detect preferably slow-growing and therefore relatively less malignant carcinomas (length-biased sampling). The bias introduced by the second factor should be the most important in a comparison of tumour size and stage of disease between a clinical series and a screened series. Despite this disadvantage, which will be discussed later, such a comparison may suggest what might be expected in future mortality analysis.

The city of Malmö has approximately 237 000 inhabitants (January 1979). The whole city is served by one general hospital, where all cases of breast carcinoma are diagnosed and treated. This facilitated a complete coverage of all women with breast carcinoma and belonging to the birth cohorts in question. In 1978 on the average 3.2 per cent of the women moved out of the city. The percentage was higher for the youngest group (4.4 %) and smaller (2.3%) for the aged. No attempt was made to trace cases of breast carcinoma in women who moved out of the city.

The incidence in the control group, 2.4 per thousand, was not markedly different from that in the beginning of the 70s, 1.9 per thousand (LINELL et coll.) and may be explained by difference in diagnostic methods used and factors such as the awareness of the population on breast problems and the availability of medical service. Mammary radiography which was introduced in Malmö 1973, undoubtedly contributed to the incidence of carcinoma diagnosed.

The higher incidence and proportion of advanced disease in the non-participants than in the controls suggest some degree of selectivity in those who decided not to participate. It was

apparent that some of the non-participants with large tumours had noticed a lump already at the time of the invitation to screening. This might imply that advanced disease in the entire group invited was concentrated among the non-attenders. This also points to the importance of a thorough follow-up of non-attenders and to the fact that in future mortality analyses the entire invited group be compared with the control group.

The rate of interval carcinomas depends not only on the sensitivity of the screening procedure, but also on the diagnostic facilities available to the population and the inclination to seek advice for breast complaints. If radiography had not been available, the number of interval carcinomas would have been reduced by 3 and the incidence would have been 0.5 per thousand. The interval carcinomas comprise different subgroups, one of which consists of rapidly growing tumours. In the present series 4 tumours were regarded as being of a rapidly growing type with a volume doubling time of less than 50 days.

The most striking difference between carcinomas in the control group and those detected at screening was the larger proportion of non-invasive and small invasive (≤ 10 mm) ones in the latter group. The rate of axillary metastases was considerably lower, and the proportion of stage I disease considerably higher, among women with carcinoma detected at screening. However, it was remarkable that, in spite of a smaller median size of metastasizing carcinoma in the screened group than in the control group, the proportion with at most 3 nodes involved was equally large in both groups. The same was true for the proportion with penetration of the node capsule.

Another important finding was the larger proportion of highly differentiated tubular carcinoma in the screening series than in the clinical series. Similar results have been reported by PATCHEFSKY et coll (1977). Tubular carcinoma has been considered a relatively 'benign' form of carcinoma with an excellent prognosis (COOPER et coll. 1978, OBERMAN & FIDLER 1979). This raises the important question whether radiographic screening preferably

detects relatively innocent carcinomas, leaving the more malignant ones undetected. However, the comprehensive report on the microscopic analysis by LINELL et coll. led to the conclusion that the highly differentiated tubular carcinoma represents one stage in an evolution starting with a 'radial scar', which develops into highly differentiated tubular carcinoma, which in turn progresses into less differentiated 'ductal' carcinoma. The frequency distribution of the various types of tubuloductal carcinoma (Table 6) seems to be compatible with such a hypothesis. Thus, the investigation by LINELL et coll. clearly supports the view that the large proportion of tubular carcinomas found at screening is an expression of early diagnosis of ductal carcinomas. This reasonably applies also to at least some of the radial scars, which were found in 12 per cent of the benign biopsy specimens in the screening series (ANDERSSON 1980). The radial scar as well as the small tubular carcinoma is characterized by marked retraction of structures towards the centre of the lesion, facilitating its detection at radiography. There is evidence that all tubuloductal carcinomas start in radial scars (LINELL et coll.).

The invasive comedocarcinoma, which represented the second largest group of invasive carcinoma is probably preceded by intraductal carcinoma in situ (MUIR 1941, GALLAGER & MARTIN 1969). This might help to explain the difference in frequency of invasive comedocarcinoma and intraductal carcinoma in situ in the screened series and in the clinical series. Some of these tumours apparently have a radiographically detectable early stage characterized by calcifications.

It is not known whether all or how many radiographically demonstrated carcinomas in situ can progress to invasive comedocarcinoma. It is, however, clear that some invasive comedocarcinomas are not preceded by radiographically identifiable intraductal carcinoma in situ with calcifications.

Invasive carcinoma of 'comedo' type as well as medullary carcinoma with lymphoid infiltration and mucinous carcinoma all tend to form sharply delineated tumours, making them less readily

detectable at an early stage than tubular carcinoma, which almost always forms spiculated tumours. This may at least in part explain the smaller proportion of these types of carcinoma in the screening series. This explanation is supported by the fact that of 11 interval carcinomas diagnosed within one year of the screening, one was a medullary carcinoma with lymphoid infiltration, one was partly medullary and one a comedocarcinoma.

The third largest group of invasive breast carcinoma, the invasive lobular carcinoma, probably originates in lobular carcinoma in situ (FOOTE & STEWART 1941, MUIR), whose radiographic appearance is not characteristic.

Concluding remarks

Radiographic screening for breast carcinoma yields a sample which deviates from a clinical series in a definable way as far as size, rate of axillary metastases, stage of disease and microscopic type are concerned, but it is not known how these differences affect the prognosis. Thus, it is not known whether a 10 mm tumour detected at radiography is biologically equivalent to a tumour of the same size found at physical examination. However, available data do not support the view that the screening sample consists of preponderantly innocent carcinomas, but rather that the screening detects average tumours in an earlier stage. Probably, the most reliable method to assess the effect of radiographic screening is to evaluate the mortality in a long-term follow-up of a randomized series.

Summary

Prognostic markers were analysed in a randomized screening project for breast carcinoma using mammary radiography as the only screening method. The proportion of small carcinomas (non-invasive and invasive at most 10 mm across) was significantly larger among carcinomas detected at screening than that of carcinomas appearing in the control group. Furthermore, the rate of axillary metastasis was lower and the proportion of stage I disease significantly larger. The proportion of highly differentiated tubular carcinoma and intraductal carcinoma in situ was

significantly larger in the screened group, while the proportion of less differentiated tubuloductal carcinoma, invasive comedo-carcinoma and medullary carcinoma with lymphoid infiltration was larger in the comparison group. The findings strongly indicate that carcinomas found at radiographic screening represent, on the average, an earlier stage compared with carcinomas detected in clinical practice.

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From the Departments of Diagnostic Radiology and Preventive Medicine, University of Lund. Malmö Allmänna Sjukhus, S-214 01 Malmö, Sweden.

RADIOGRAPHIC SCREENING FOR BREAST CARCINOMA

III. Appearance of carcinoma and number of projections to be used at radiography.

I. Andersson

According to most authors, the prognosis of breast carcinoma is related to the size of the tumour and the state of the axillary lymph nodes at the time of treatment (PAYNE et coll. 1970, ADAIR et coll. 1974, SAY & DONEGAN 1974, DUNCAN & KERR 1976, WALLGREN et coll. 1976, ATTIYEH et coll. 1977). Patients with minimal tumours as defined by GALLAGER & MARTIN (1971), i.e. carcinoma in situ, intraductal as well as lobular, and invasive carcinoma ≤ 5 mm in diameter, have been reported to have a 20-year actuarial survival rate of 93 per cent (FRAZIER et coll. 1977). Patients with invasive carcinoma at most 10 mm across were reported to have a 20-year survival rate of 80 per cent (DUNCAN & KERR). On the other hand, KREYBERG & CHRISTIANSEN (1953) did not find small carcinomas (< 15 - 17 mm) to be associated with a particularly favourable prognosis.

Invasive carcinoma ≤ 10 mm as well as carcinoma in situ are rarely palpable. At present, mammary radiography is the only sensitive method for demonstrating carcinomas of this size. It is therefore essential to be familiar with the radiographic appearance of small carcinomas.

The radiographic characteristics of mammary carcinoma are described in several textbooks (GROS 1963, EGAN 1970, GERSHON-COHEN 1970, WOLFE 1972, HOFFKEN & LANYI 1973, BARTH 1977, FRISCHBIER & LOHBECK 1977, WOLFE 1977 a, b) and in a recent thesis (BJURSTAM 1978). The present report is a retrospective analysis of a consecutive series of mammary carcinoma detected at radiographic screening with reference to dominating radioiographic abnormality in relation to the size of the carcinoma. Furthermore, the aim was to analyse the visibility of these abnormalities in the different projections used and in relation to the size of the lesions.

MATERIAL AND METHODS

Between January 1977 and September 1978 the first round of a cross-sectional breast tumour screening of women, aged 45 to 69 years and living in the city of Malmö, was completed. Mammary radiography was the only screening method. A total of 21 242 women were invited. Altogether 15 748 (74 %) accepted. Carcinoma was detected in 118 (7.5 per 1000). One woman, in whom only a craniocaudal view had been obtained, refused further examination. This left 117 patients for the present investigation. The age distribution is given in Table 1.

Two views, craniocaudal and oblique, were obtained with the patient standing. For the oblique projection the beam was directed about 45° laterally. Efforts were made to include the breast and as much as possible of the axilla. If the examination revealed abnormalities suggesting carcinoma, the woman was recalled for re-examination, which usually included one or more

Table 1. Age distribution of patients according to size of the carcinoma. CIS = carcinoma in situ, IC = invasive carcinoma

Age	CIS	IC $\leq$ 10 mm	IC > 10 mm	Total
45-49	2	7	5	14
50-54	4	10	9	23
55-59	2	8	11	21
60-64	3	14	12	29
65-69	8	11	11	30
45-69	19	50	48	117

films in the 3 standard projections, craniocaudal, oblique and lateromedial. Occasionally additional films were exposed in projections differing by about 10° from the standard ones. Coned-down views were obtained when indicated.

A Philips Diagnost M was used operating at 28 kV. Film-focus distance was 50 cm.

Various film-screen combinations were used, mostly the Kodak Min-R system or Agfa-Gevaert MR 50 screens combined with Scopix film. The films were developed automatically at 31° C; the developer was G 137 (Agfa Gevaert), and developing time 57 seconds. Processing time was 4.5 min. The mean absorbed dose per exposure was 1 mGy, measured with thermoluminescent dosimeters (LiF-teflon).

The following radiographic abnormalities were considered suggestive of carcinoma.

- (1) A *tumour mass* with an irregular or poorly defined border with or without retraction of tissue strands (called spiculation by several authors) towards the tumour. Also a rounded, nodular or lobulated mass, mainly well outlined but poorly defined in some part of the periphery. Although not decisive the attenuation of a tumour was also taken into account, high attenuation speaking for the tumour being malignant.
- (2) Distortion of the normal architecture of the breast, usually in the form of *retraction* of the structures in a stellate manner, but without a dominating tumour mass.
- (3). Irregular *calcifications*, i.e. calcifications of varying form and size, arranged either disorderly or in a linear fashion, and appearing either in one or more clusters or dispersed in one or more segments of the breast. Obviously benign irregular calcifications such as those occurring in plasma cell mastitis, fibroadenoma and in the walls of arteries were ignored.

In each case one of the above abnormalities (1 - 3) was considered as the most important for the suggestion of malignancy. Notes were also made of any thickening and retraction of the skin and nipple, however, without use of special projections for demonstrating such lesions.

In order to grade the visibility of the abnormalities, each film was given a score according to the following scale: 0 = no indication of malignancy, 1 = uncertain malignancy, 2 = suggestive or evident indication of malignancy. The screening films were reviewed by 2 experienced radiologists to test the observer variation. The films were arranged in pairs, so that the cranio-caudal projection of the right breast and that of the left were presented together as were the films in the oblique projection. The films of the patients were mixed with the screening films of 100 women without carcinoma. These films had been randomly selected from the files, 20 within each quinquennium. All pairs of films were then mixed to prevent the films in cranio-caudal and oblique projection of one and the same patient from being reviewed consecutively. The number of subjects with and without malignant tumours was not known to the reviewers.

The material was divided into 3 groups of specimens at microscopy: (1) carcinoma in situ (2) invasive carcinoma with a diameter of at most 10 mm and (3) those with a diameter of more than 10 mm as measured on the specimens or, in 5 cases on the films. The largest diameter was recorded.

RESULTS

Dominating radiographic abnormality suggesting malignancy. In 68 (58 %) cases a *tumour mass* was the dominating abnormality suggesting carcinoma (Table 2). All but one were invasive. A mass was the dominating abnormality in 50 per cent of invasive carcinoma with a diameter of ≤ 10 mm and in 88 per cent of those with a diameter of > 10 mm. The tumour was irregular in outline with or without retraction of the surrounding structures in 66 of the 68 cases. In 10 of these cases the tumour was partly and in 2 cases mainly smooth.

Table 2. Dominating radiographic abnormality suggesting carcinoma.

	Tumour mass		Retraction		Calcific.	Total
	No.	(%)	No.	(%)	No. (%)	No. (%)
CIS	1	(5)			18 (95)	19 (100)
IC $\leq$ 10 mm	25	(50)	10 (20)		15 (30)	50 (100)
IC > 10 mm	42	(88)	3 (6)		3 (6)	48 (100)
TOTAL	68	(58)	13 (11)		36 (31)	117 (100)

Calcifications were found in the tumour mass in 16 (24 %) cases. Calcifications were more common in large tumours (14/42, 33 %) than in small tumours (2/25, 8 %).

Retraction was the dominating abnormality in 13 cases (11 %, Table 2, Fig. 1). In ten cases with invasive carcinoma the tumour was $\leq$ 10 mm and in 3 cases > 10 mm. Retraction was never the main abnormality in carcinoma in situ. In 9 cases at least

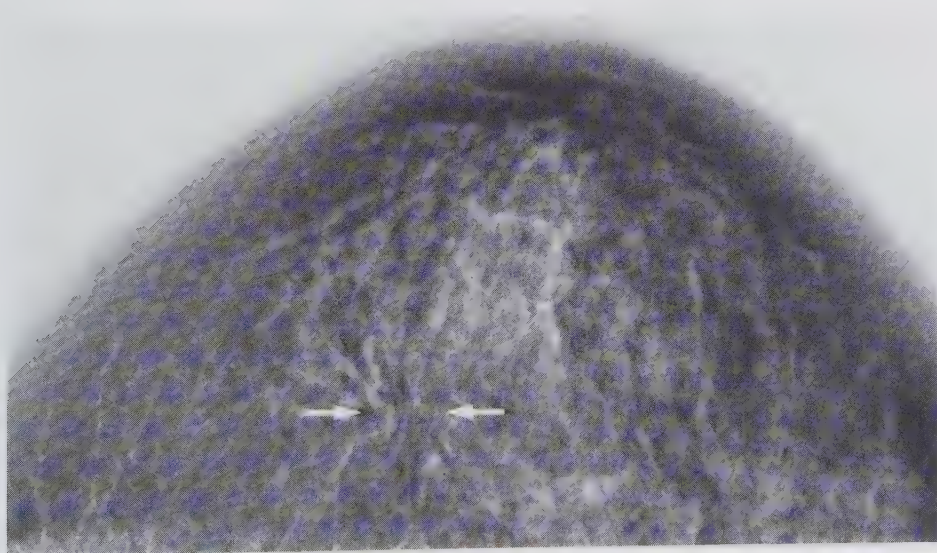


Fig. 1. Distorsion of the structures which are retracted in a stellate manner (arrows). No discrete tumour mass. Microscopy revealed a pure tubular carcinoma measuring 4 mm.

one projection showed a tumour in the centre of the retraction. These tumours were situated in dense parenchyma and were identifiable only due to the retraction. In 2 cases also calcifications were found.

Calcifications were the main abnormality indicating carcinoma in 36 cases (31 %, Table 2). All but one of the cases of carcinoma in situ (95 %) were betrayed by the presence of calcifications. In 12 of these cases the calcifications were combined with unspecific soft tissue abnormalities which in 3 had the appearance of dilated ducts (Fig. 2). In 6 cases no abnormality of the soft tissues were seen, but the calcifications were situated in generally dense tissue. In one case the calcifications were combined with retraction. This lesion represented a radial scar (LINELL et coll. 1980).

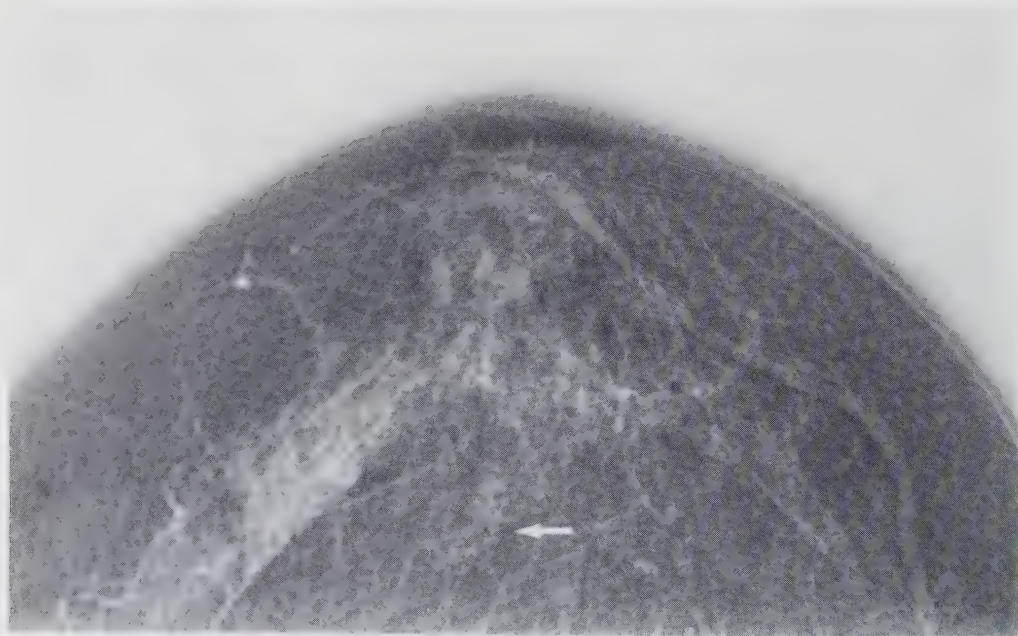


Fig. 2. Irregular calcifications localized in an area with moderately increased attenuation, probably representing dilated ducts (arrow). Microscopy revealed an intraductal carcinoma in situ.

Sixteen of the cases of carcinoma in situ were intraductal and 3 were lobular. The finding of these latter 3 cases was incidental. In one of the cases the calcifications were confined to an area of sclerosing adenosis adjacent to the lobular carcinoma in situ and, in the other 2, most of the calcifications were situated in dilated ducts in areas of cystic mastopathy adjacent to the lobular lesion. The calcifications in these 3 cases were more rounded and fuzzy in outline than those occurring in typical cases of intraductal carcinoma.

Fifteen cases of invasive carcinoma ≤ 10 mm (30%) were betrayed by calcifications. In these cases either no tumor mass was apparent or a mass of uncharacteristic appearance (Fig. 3). In 3 cases the calcifications represented a non-cancerous lesion, in the first a fibroadenoma; in the second, dilated ducts with

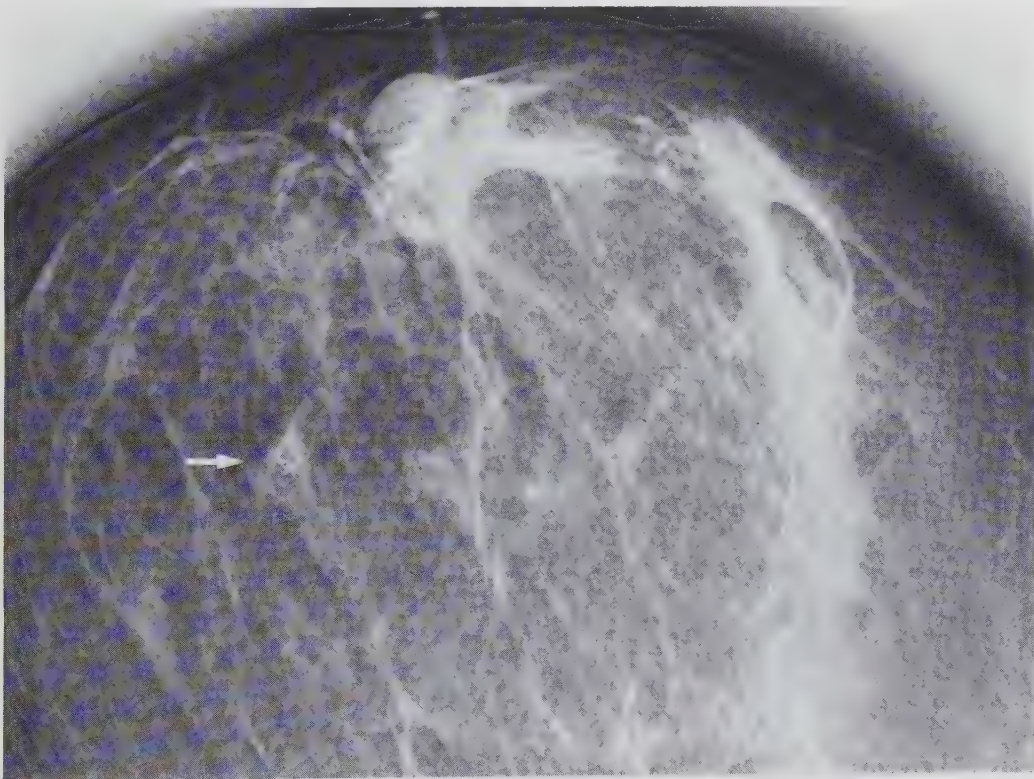


Fig. 3. Irregular calcifications localized in a mass with quite uncharacteristic appearance (arrow). Microscopy: invasive comedocarcinoma measuring 10 mm.

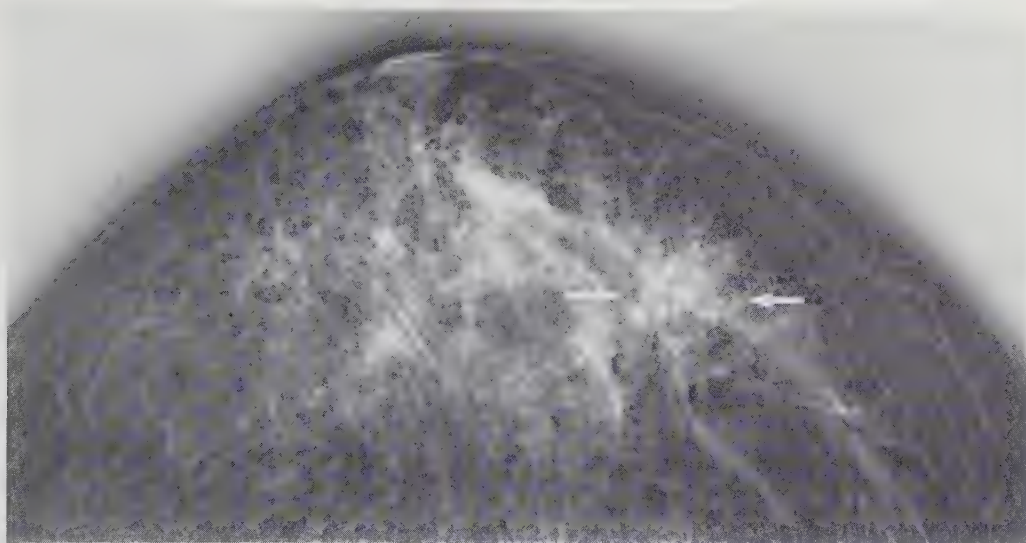
inspissated material (Fig. 4); and in the third, sclerosing adenosis. In all 3 cases an invasive carcinoma was found adjacent to the benign lesions.

Three cases of invasive carcinoma > 10 mm (6 %) were betrayed mainly by the presence of calcifications. In 2 cases no discrete tumour mass was apparent (Fig. 5). In these cases the parenchyma was rather dense. In the third case the calcifications were confined to a mass-like uncharacteristic area with a high attenuation.

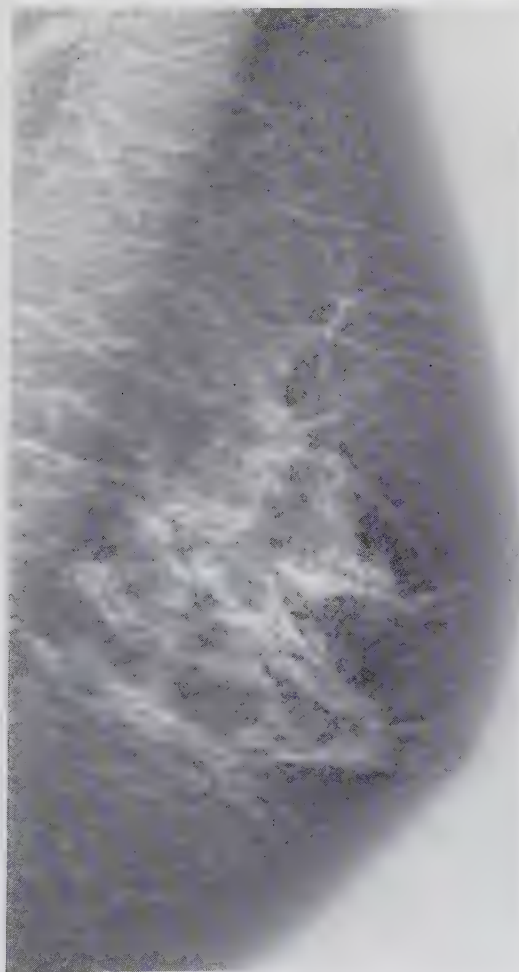
Skin and nipple abnormalities. Local thickening of the skin, retraction of the skin or retraction of mamilla occurred in altogether 26 patients (22 %). Thirteen of these had more than one abnormality. It is apparent from Table 3 that abnormality of the



Fig. 4. Irregular calcifications scattered in a rather large area of the breast. No discrete tumour mass. At microscopy calcifications were found in inspissated material in dilated ducts and incidentally an invasive comedocarcinoma measuring 5 mm.



A



B

Fig. 5. A. Craniocaudal, B. oblique projection. A few calcifications are seen but no clear clear tumour mass. Some retraction of the structures towards the area with calcifications is evident in A (arrows). Microscopy: invasive ductal carcinoma (tubuloductal type; Linell et al 1980) measuring 20 mm; metastases in 7 axillary lymph nodes with perinodal growth in 5.

skin and nipple did not occur in carcinoma in situ and were considerably more frequent in invasive carcinoma > 10 mm compared with those ≤ 10 mm.

Table 3. Changes of the skin and nipple. Figures within brackets denote per cent

	No. of patients	Retraction of the skin	Thickening of the skin	Retraction of the nipple
CIS	19	-	-	-
IC ≤ 10 mm	50	2 (4)	3 (6)	3 (6)
IC > 10 mm	48	13 (27)	10 (21)	12 (25)
TOTAL	117	15 (13)	13 (11)	15 (13)

Tumour demonstration in the different projections. At the initial screening 234 films were obtained of 117 breasts with carcinoma and a further 317 at the complete radiographic examinations, i.e. altogether 551. At the retrospective analysis every film was given a score of 0-2. The results of the analysis are given in Tables 4 through 9.

It is evident from Table 4 that 89 and 91 per cent of the carcinomas were considered as probable or certain carcinoma (score 2) in the craniocaudal and in the oblique projection, respectively. The two reviewers classified 86 to 87% per cent accordingly (Tables 5, 6). The size of invasive carcinoma was correlated to its visibility; those ≤ 10 mm received a score of 2 in 76 to 86 per cent of the cases, those ≥ 10 in 90 to 94 per cent. Thirteen of 16 tumours demonstrated in only one projection were invasive carcinoma ≤ 10 mm. The corresponding proportions for the two reviewers were 13/18 and 17/21, respectively. It is also apparent that a score of 0 was most common in the craniocaudal projection. Furthermore, one of the reviewers gave 6 % of the non-cancerous cases a score of 1, while the other gave 6% a score of 1 and another 2% a score of 2. At the second screening none of these women were suggested to have carcinoma.

Table 4. Visibility of the carcinomas on the screening films (I.A.)
Figures within brackets denote per cent

	No. of patients	Craniocaudal projection			Oblique projection		
		0	1	2	0	1	2
CIS	19			19(100)			19(100)
IC $\leq$ 10 mm	50	8(16)	2 (4)	40 (80)	5(10)	2(4)	43 (86)
IC > 10 mm	48	1 (2)	2 (4)	45 (94)	2 (4)	1(2)	45 (94)
TOTAL	117	9 (8)	4 (3)	104 (89)	7 (6)	3(3)	107 (91)

Table 5. Visibility of the carcinomas on the screening films (B.N.)
Figures within brackets denote per cent.

	No. of patients	Craniocaudal projection			Oblique projection		
		0	1	2	0	1	2
CIS	19			19 (100)			19 (100)
IC $\leq$ 10 mm	50	9 (18)	3(6)	38 (76)	4 (8)	7 (14)	39 (78)
IC > 10 mm	48	3 (6)	1(2)	44 (92)	2 (4)	3 (6)	43 (90)
TOTAL	117	12 (10)	4(4)	101 (86)	6 (5)	10 (9)	101 (86)

Table 6. Visibility of the carcinomas on the screening films (H.P.)
Figures within brackets denote per cent

	No. of patients	Craniocaudal projection			Oblique projection		
		0	1	2	0	1	2
CIS	19			19 (100)			19 (100)
IC $\leq$ 10 mm	50	10 (20)	2 (4)	38 (76)	7 (14)	5(10)	38 (76)
IC > 10 mm	48	2 (4)	1 (2)	45 (94)	2 (4)	1 (2)	45 (94)
TOTAL	117	12 (10)	3 (3)	102 (87)	9 (8)	6 (5)	102 (87)

Clear indication of carcinoma was demonstrated on 89 per cent of the total number of films taken in craniocaudal projection and on 88 and 83 per cent, respectively, of the films taken in the oblique and the lateromedial projection (Tables 7 - 9). Carcinoma in situ was demonstrated on all films. Invasive carcinoma ≤ 10 mm was definitely demonstrated on 75 to 84 per cent of the films while those > 10 mm were clearly demonstrated on 86 to 95 per cent of all films in the different projections.

The 25 films taken in the craniocaudal projection with a score of 0 and 1 (Table 7) refer to 15 patients. Twelve of these patients had a varying score on successive films. In 5 cases the difference was 2 points, which means that the carcinoma was definitely demonstrated on one film and not on another film in the same or approximately the same projection. In 7 patients the difference was 1 point.

Table 7. Visibility of the carcinomas in craniocaudal projection.
Figures within brackets denote per cent

	No. of patients	No. of films	Score (films with)		
			0	1	2
CIS	19	27			27 (100)
IC ≤ 10 mm	50	110	14 (13)	7 (6)	89 (81)
IC > 10 mm	48	86	1 (1)	3 (4)	82 (95)
TOTAL	117	223	15 (7)	10 (4)	198 (89)

The 23 films with a score of 0 or 1 in the oblique projection (Table 8) refer to 18 patients, whose films showed a difference of 2 points in 2 and of 1 point in 5.

In the lateromedial projection 23 films with a score of 0 or 1 refer to 19 patients, in one of whom the difference was 1 point (Table 9).

Table 8. Visibility of the carcinomas in oblique projection
Figures within brackets denote per cent

	No. of patients	No. of films	Score (films with)		
			0	1	2
CIS	19	23			23 (100)
IC $\leq$ 10 mm	50	100	11 (11)	5 (5)	84 (84)
IC > 10 mm	48	73	3 (4)	4 (5)	66 (91)
TOTAL	117	196	14 (7)	9 (5)	173 (88)

Table 9. Visibility of the carcinomas in lateromedial projection.
Figures within brackets denote per cent

	No. of patients	No. of films	Score (films with)		
			0	1	2
CIS	19	20			20 (100)
IC $\leq$ 10 mm	50	63	10 (16)	6 (10)	47 (75)
IC > 10 mm	48	49	2 (4)	5 (10)	42 (86)
TOTAL	117	132	12 (9)	11 (8)	109 (83)

Table 10 includes all patients with a score of 0 or 1 on any one film. It is evident that the proportion of patients with a score of 0 or 1 decreased with age.

Table 10. Age distribution of patients with score 0 and/or 1.

Figures within brackets denote percentages of total number of carcinomas in age-group.

Age group	45 - 49	50 - 54	55 - 59	60 - 64	65 - 69	45 - 69
CIS	0	0	0	0	0	0
IC $\leq$ 10 mm	1 (14)	7 (70)	6 (75)	3 (21)	2 (18)	19 (38)
IC > 10 mm	5 (100)	0	1 (9)	1 (8)	1 (9)	8 (17)
TOTAL	6 (43)	7 (30)	7 (33)	4 (14)	3 (10)	27 (23)

The reason why the the tumours were not demonstrated or difficult to identify was, in 23 cases, either superimposition of tissue with a high attenuation or unspecific appearance of the tumour, not differing from the parenchyma (Figs 6, 7). In 4 cases the tumour was situated juxtathoracically and therefore not included on the films (Fig. 8).

A

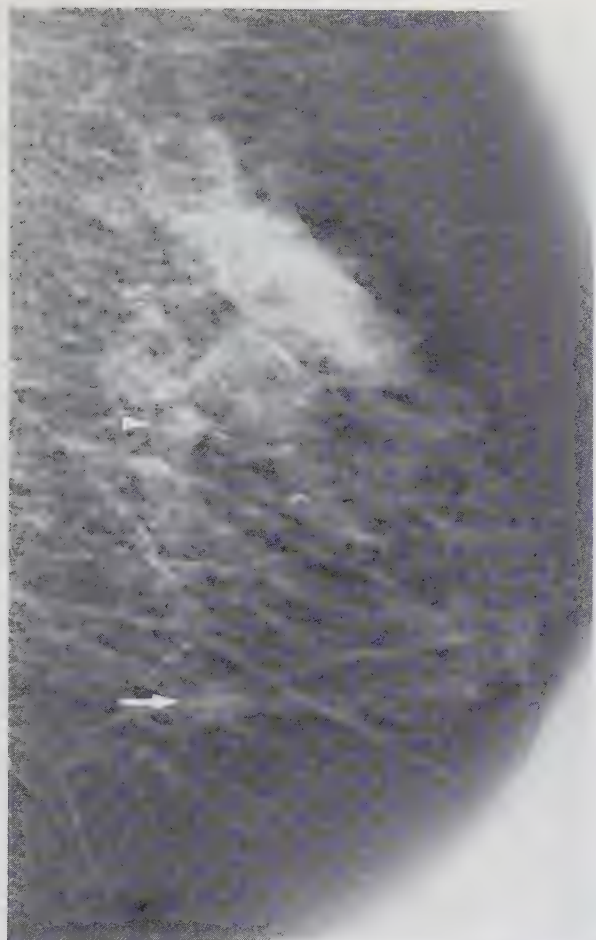
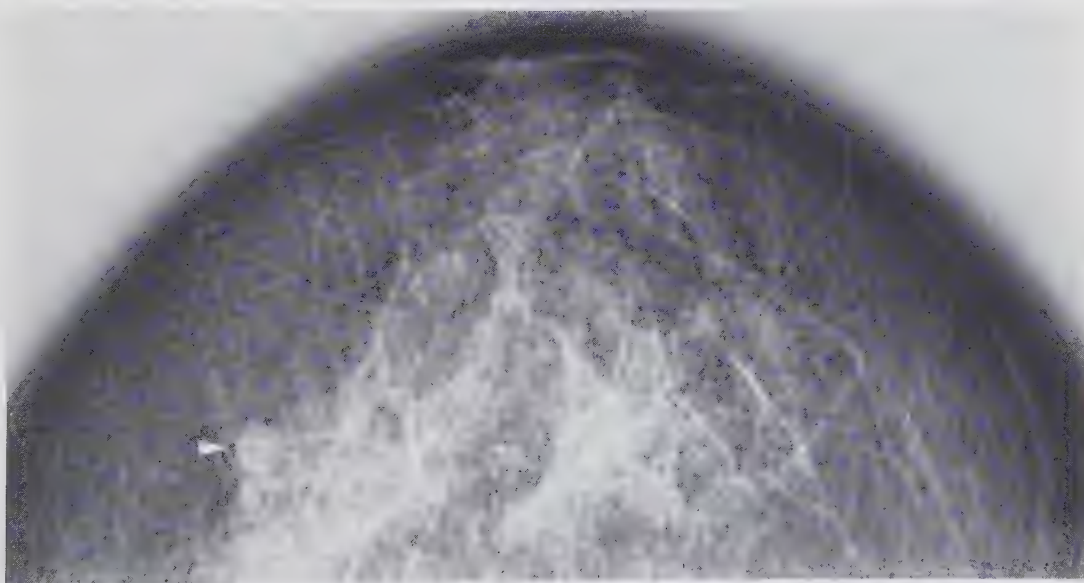
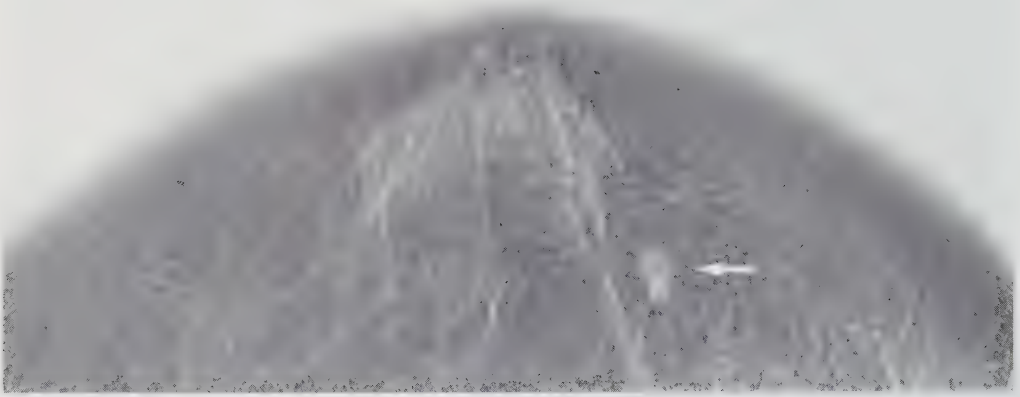


Fig. 6. An irregular, highly suspicious tumour (arrow) is seen in the oblique projection (A) but not in the craniocaudal projection (B). In both projections a well circumscribed, benign tumour is demonstrated (arrow-head). At microscopy the irregular tumour was found to represent a pure tubular carcinoma measuring 8 mm.

B





A



Fig. 7. In the craniocaudal projection (A) a typical carcinoma is demonstrated (arrow). In the oblique projection (B) the appearance of the tumour is quite uncharacteristic (arrow). Microscopy: pure tubular carcinoma measuring 7 mm.

B



A

Fig. 8. In the craniocaudal projection (A) a typical carcinoma is seen in the medial, juxtathoracic part of the breast. In the oblique projection (B; overleaf) only some distorted tissue strands are seen (arrows). Microscopy: invasive tubular carcinoma with "ductal" structures (Linell et al, 1980) measuring 14 mm.

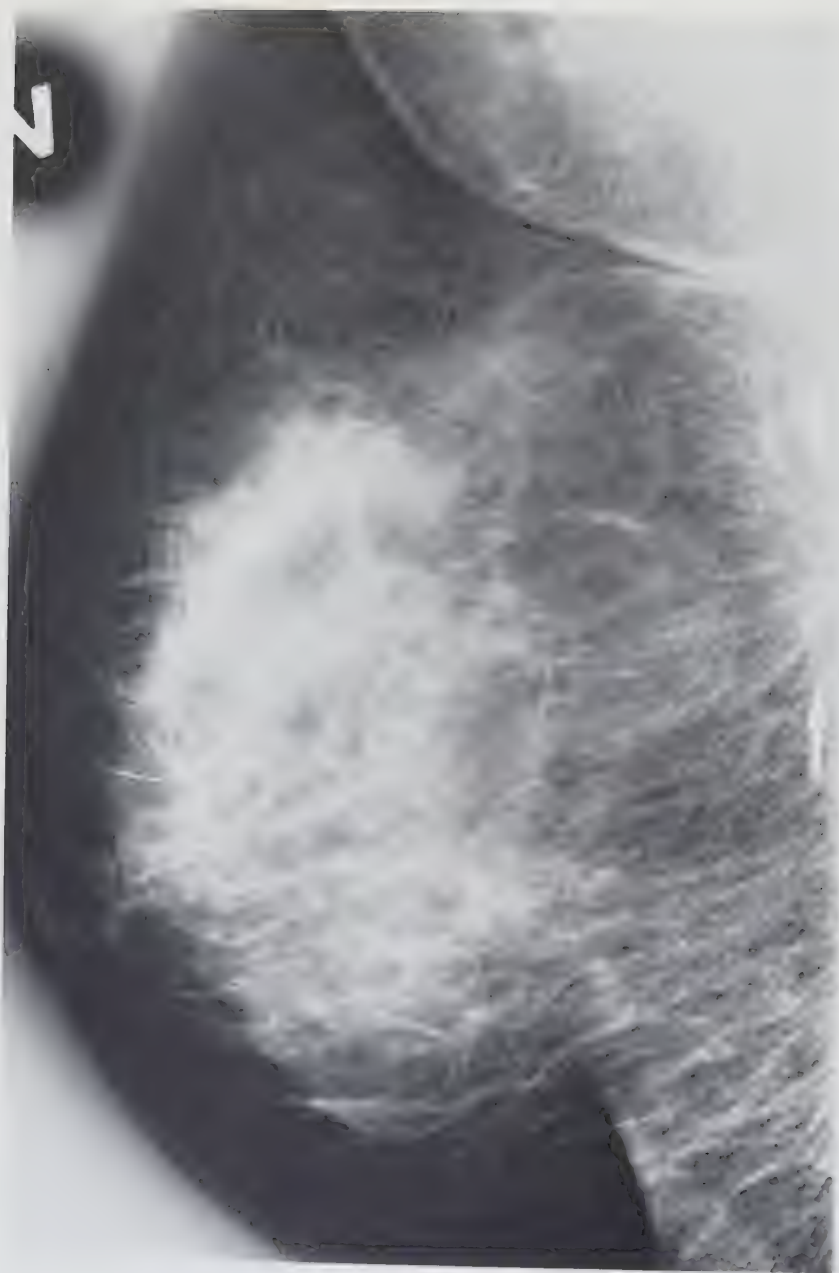


Fig. 8 B

DISCUSSION

The present material consisted of a consecutive series of carcinomas detected at radiographic screening of an unselected population, aged 45-69. Mammary radiography was the sole screening mode. Compared with clinical series the material is characterized by a substantially larger proportion of small carcinomas.

On the basis of the histopathologic examination the material was divided into what may be regarded as broad prognostic groups. According to LANGLANDS & KERR (1978), the size of the tumour is the most important prognostic factor. Carcinomas not exceeding 10 mm in diameter are considered to have a good prognosis (KERN & MIKKELSEN 1971, DUNCAN & KERR). None of the patients in the present series with carcinoma in situ were known to have axillary metastases, 3 (6%) of 50 patients with invasive tumours $\leq$ 10 mm had axillary metastases and 18 (38%) out of 48 patients with invasive carcinoma $>$ 10 mm.

A tumour diameter of 10 mm may be regarded as the borderline between palpable and non-palpable carcinomas. In the present material the clinical examination was performed with knowledge of the radiographic findings. In the combined group of carcinoma in situ and invasive carcinoma $\leq$ 10 mm, 56 (81%) of 69 were either not palpable or appeared to be a benign lesion. In the group of carcinomas $>$ 10 mm the corresponding figure was 11 (23%) of 48.

An attempt was made to decide which radiographic abnormality was the most important for the diagnosis of carcinoma. In some cases with more than one abnormality, e.g. tumour mass and calcifications, each abnormality per se would have led to a correct diagnosis. Generally, a tumour mass was the most frequent finding suggesting invasive carcinoma, and especially those $>$ 10 mm, while calcifications were almost the only abnormality suggesting carcinoma in situ. Naturally, the smaller the tumour the less dominating it was as a mass and the more important were retraction and calcifications for the diagnosis. Thus, 25 (50%)

of 50 cases with invasive carcinoma ≤ 10 mm were betrayed mainly by retraction and calcifications, compared with only 12 per cent of those > 10 mm.

The importance of calcifications in the diagnosis of early breast carcinoma has often been emphasized. In a series of clinically occult carcinomas (mainly asymptomatic women) reported by FRISCHBIER & LOHBECK, calcifications were the dominating abnormality in 29 per cent ($n = 62$), a tumour mass in 58 per cent, and a tumour associated with calcifications in the remaining cases. MENGES et coll. (1976) reported that 42 per cent of occult carcinomas ($n = 47$) were betrayed by calcifications and 28 per cent by a tumour mass. BJURSTAM found that 37 per cent of non-palpable carcinomas ($n = 27$) appeared as calcifications alone, while the corresponding figure for palpable carcinomas was 2 per cent ($n = 133$). In a series consisting mainly of symptomatic women WOLFE (1974) considered calcifications as the main abnormality in 37 per cent of non-palpable carcinomas ($n = 139$) and in 6 per cent of palpable carcinomas ($n = 301$). LUNDGREN (1978) observed calcifications in 31 per cent of 302 carcinomas (symptomatic and non-symptomatic women, $n = 294$) but calcifications were the sole indication of malignancy in only 3.6 per cent. LUNDGREN found no significant difference in the frequency of calcifications between carcinomas detected at radiography alone and those detected at both radiography and clinical examination.

In the present series calcifications were by far the most important abnormality suggesting carcinoma in situ. Also, a fairly large proportion of invasive carcinoma ≤ 10 mm were betrayed by calcifications. However, it should be emphasized that in 70 per cent of invasive carcinoma ≤ 10 mm a tumour mass or retraction decided the diagnosis.

Abnormal skin and nipple were occasionally found in breasts with invasive carcinoma ≤ 10 mm. BJURSTAM found such lesions in as many as 25 per cent of his cases. The difference may be explained

by the fact that BJURSTAM used special projections to demonstrate the skin area above the tumour, which was not done in the present series.

An important finding was the inconsistent radiographic appearance of invasive carcinoma. This applied above all to those ≤ 10 mm which were betrayed mainly by a tumour mass, while those betrayed by calcifications were consistently observed in the various projections and in successive films in the same projection. In several cases the radiographic examination showed what seemed to be a characteristic change in one projection but not in another. The results indicate that 10 to 20 per cent of invasive carcinoma ≤ 10 mm would have been overlooked if only one projection had been used at screening. When also the films taken at the complete radiographic examination were analysed, approximately the same percentage of films in the craniocaudal and oblique projections still got a score of 0 or 1. This means that the chances of finding a carcinoma, and particularly an invasive carcinoma ≤ 10 mm, varies with the number of films obtained.

The screening material does not permit evaluation of the craniocaudal projection alone, since the craniocaudal projection was directed so as to include as much as possible of the medial, juxtathoracic part of the breast, with the result that the lateral, juxtathoracic part was not included on the film. This part of the breast was covered by the oblique projection. In a previous analysis no significant difference was found in the frequency of malignant changes demonstrated on any single projection (ANDERSSON et coll. 1978). Screening using a single view, i.e. the oblique projection, was introduced by LUNDGREN & JAKOBSSON (1976). In a retrospective analysis of a series of symptomatic as well as asymptomatic patients with breast carcinoma ($n = 392$) LUNDGREN (1977) found that 95 per cent of the carcinomas were demonstrated in the oblique projection, the corresponding figures for the craniocaudal and lateral projections were 81 and 80 per cent. A single view was also advocated by WEISHAAR et coll. (1976) who recommended the oblique projection and BUCHANAN & JAGER (1977) who recommended the mediolateral

view (xeromammography). CUKIER et coll. (1977) considered the lateral projection to be sufficient for follow-up unless the breast tissue was relatively dense.

On the other hand, LIBSHITZ et coll. (1976), MOSKOWITZ & LIBSHITZ (1977) and HÜPPE & SCHNEIDER (1977) considered a single view insufficient. In a review of symptomatic patients ($n = 62$) LIBSHITZ et coll. found that on the craniocaudal view 6 per cent of the carcinomas were missed and, on the lateral 3 per cent, respectively. Another 5 per cent were equivocal. Of 23 carcinomas found at screening 22 and 4 per cent were missed on the craniocaudal and lateral view, respectively, while 17 per cent were equivocal.

HÜPPE & SCHNEIDER compared retrospectively the efficacy of the oblique projection with that of the oblique plus the craniocaudal projection. They found that 71 per cent of 277 carcinomas were definitely demonstrated in the oblique projection. When also equivocal cases were included the figure was 87 per cent. With 2 projections 96 per cent of the carcinomas were found. When only tumours in stages T_0 and T_1 were considered, 63 per cent were clearly demonstrated in the oblique projection. The figure rose to 81 per cent when equivocal cases were included. With 2 projections 90 per cent of the carcinomas were demonstrated.

In a retrospective investigation of symptomatic patients ($n = 491$), most of whom with palpable tumours, 90 per cent of the carcinomas could be detected on a single view (ANDERSSON et coll.) without significant difference between the craniocaudal, oblique and lateromedial projections. With 2 projections 94 per cent of the carcinomas could be detected and with 3 projections 95 per cent. Five per cent of the carcinomas were not demonstrated in any of the projections.

It is important to keep the rate of false positive findings as low as possible in a screening project. Undue anxiety is induced in women who are falsely suggested of having breast carcinoma.

It is reasonable to assume that the use of a single projection will result in a higher rate of false positive findings than that of two projections. This assumption is corroborated by the fact that the two reviewers had a false positive rate of 6 and 8 per cent, when the two views used at screening were not simultaneously available. The actual rate at screening was 2.6 per cent.

The technical quality of the radiographic images is of utmost importance for the detection of small carcinomas. It is considered that the image quality in the present series was at least of average standard for the screen-film systems used. This view is also supported by the detection rate of 7.5 per 1 000. The detection rate is influenced also by a number of factors other than the sensitivity of the screening method, such as principles of selection of the women to be screened and the natural incidence rate of breast carcinoma. These factors must be taken into account when different materials are compared. In screening projects in other regions of this country with lower incidence rate the detection rate at the initial screening was between 3.7 and 7 per cent in the age-groups 40 to 69 years (LUNDGREN & JAKOBSSON, LUNDGREN 1979, FAGERBERG 1980, TABÁR et coll.) In these projects single-view radiography was used.

Concluding remarks. The dominating abnormality of non-invasive carcinoma was calcifications without a tumour mass. Calcifications were always recognized in the different projections used. Although calcifications were important also for the detection of small invasive carcinomas (≤ 10 mm), the most frequent abnormality was a tumour mass without calcifications. The appearance of small tumour masses tended to vary between different projections and also between films exposed in the same projection. The detection of small invasive carcinomas therefore tended to vary with the number of films available. This also applied to a few larger carcinomas.

The investigation thus showed that the use of two projections instead of one reduced the frequency of false negative findings,

especially of small invasive carcinomas as well as the rate of false positive findings. Although several factors such as costs, time consumption and radiation dose must be considered in a screening program, the results argue for the use of two projections, preferably the craniocaudal and oblique, at least at the first screening. At re-screening one projection may be sufficient for women whose breasts consist mainly of fat, and thus, the films are easy to evaluate.

SUMMARY

The films of 117 patients with mammary carcinoma detected at population screening were reviewed. Sixteen per cent (19) of the women proved to have non-invasive and 43 per cent (50) small invasive carcinomas (diameter ≤ 10 mm). Calcifications were the dominating abnormality in 95 per cent of the non-invasive carcinomas, while a tumour mass was the most frequent abnormality in small invasive carcinomas. It was found that the appearance of small tumours may vary considerably from one projection to another and also on films in one and the same projection. Thus, approximately 20 per cent of small invasive carcinomas were either not visible or equivocal in one of the two projections used at screening. The corresponding figure for larger invasive carcinomas (diameter > 10 mm) was approximately 7 per cent. It is concluded that films in two projections, preferably the craniocaudal and oblique, should be obtained at screening.

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From the Departments of Preventive Medicine, Diagnostic Radiology (I.A., H.P.), and Surgery (L.J.), University of Lund, Malmö General Hospital, S-214 01, Malmö, Sweden.

RADIOGRAPHIC PATTERNS OF MAMMARY PARENCHYMA

Variation with Age at Examination and Age at First Birth

Ingvar Andersson, M.D., Lars Janzon, M.D. and Holger Pettersson, M.D.

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In 1976 Wolfe (21, 22) suggested that the roentgenographic appearance of the mammary parenchyma might be useful in the appraisal of a predisposition to carcinoma of the breast. In his classification of the breast parenchyma the groups termed N1 and P1 were associated with a substantially lower risk of breast carcinoma than the groups termed P2 and DY.

The validity of this classification has been questioned (5, 7, 13, 16), but there is now growing evidence that women with P2 and DY patterns are at increased risk for breast cancer (4, 9, 10, 14).

Several reports are available on the parenchymal patterns found in women seeking advice because of breast symptoms and in self-selected women participating in cancer detection programs, but none on the distribution of such patterns among randomly selected women representative for the female population. Information from such a cross-sectional survey would furthermore yield baseline data for a prospective study necessary for further evaluation of the reported association between breast cancer and the parenchymal patterns.

In a pilot study of 50 and 60 year-old-women (1) the percentage of women classified as P2 and DY was found to increase with age at first birth. The aim of the present investigation was to estimate the prevalence of the various parenchymal patterns according to Wolfe in relation to age and age at first birth in a representative sample of 45-69 year old women.

MATERIAL AND METHOD

A breast cancer screening project has been running since January 1977 in Malmö, a city in southern Sweden with about 240,000 inhabitants (2). Of all the women aged 45-69, one half were randomly selected and invited to roentgenographic screening of the breast; the other half served as controls. The overall rate of attendance was 74%. Mammography is the only screening method used. Various film-screen systems have been used, mostly the Kodak Min-R system or Agfa-Gevaert MR 50 screens combined with Scopix

film. Craniocaudal and oblique views were obtained. At the screening the women were asked about their age at first birth.

The present report is based on 15,110 women, representing 71% of those invited and 95% of those screened. The remaining 5% represent women whose mammograms could not be classified owing to previous mammoplasty and women whose mammograms were not available at the time the data were being fed into the computer. The mammograms were classified according to Wolfe (21, 22) by one of 3 radiologists with long experience of mammography. In the beginning of the study all the mammograms were examined jointly in an effort to standardize the classification. Breasts consisting almost entirely of fat were designated N1. Breasts with a "prominent duct pattern" in at most 25% of the breast were classified as P1 and as P2 if more than 25 % was involved. Breasts dominated by more or less homogenous areas with a density higher than that of fat were classified as DY. The examiner was unaware of the woman's age at first birth. Observer variation was studied by repeated classification of 1,000 randomly selected mammograms, which were reviewed by two of us (I.A. and H.P.). Our opinions agreed in 87.1% of the cases. As for the remaining 12.9%, there was a disagreement of 4.7% between N1 and P1, of 3.7% between P1 and P2 and of 4.5% between P2 and DY. No other discordant pairs were found.

STATISTICAL METHODS

A Chi-square 2 x 2 contingency table was used to test the following null-hypotheses:

- I. $H_0: P_{<20}(P2+DY) = P_{\alpha}(P2+DY)$, where <20 indicates first birth before 20 and α successive first birth at 20-32, over 32, and nulliparae within groups matched for age at examination, and
- II. $H_0: P_{65-69}(P2+DY) = P_{\beta}(P2+DY)$, where 65-69 indicates age at examination and β successive age-groups 45-49, 50-54, 55-59 and 60-64, within groups matched for age at first birth.

The odds ratio (6) was used to express the degree of association between the parenchymal patterns P2 + DY and respectively age at examination and age at first birth according to the following:

- I. R_{α}/R_{65-69} , where R_{65-69} is the ratio $P(P2+DY)/P(N1+P1)$ of women aged 65-69 and R_{α} is $P(P2+DY)/P(N1+P1)$ of successive age-groups 45-49, 50-54, 55-59 and 60-64 within groups matched for age at first birth and
- II. $R_{\beta}/R_{<20}$, where $R_{<20}$ is the ratio $P(P2+DY)/P(N1+P1)$ of women with first birth before 20 and R_{β} is $P(P2+DY)/P(N1+P1)$ of women with successive first birth at 20-32, over 32 and nulliparae within groups matched for age at examination.

RESULTS

In 11% of the cases the mammograms were classified as N1, in 38% as P1 in 16.2% as P2 and in 34.8% as DY (Table I). Combining N1+P1 and P2+DY, the percentages were 49% and 51%, respectively. The percentage of mammograms classified as P2+DY diminished from 66.2% in women, aged 45-49, to 41.5% in women, aged 65-69. The

Table 1. Parenchymal patterns by age (per cent)

Age	45-49	50-54	55-59	60-64	65-69	45-69
No of women	2,802	3,181	3,382	3,095	2,650	15,110
N1	5.0	9.2	10.1	14.4	16.9	11.0
P1	28.8	37.4	39.8	41.8	41.6	38.0
N1+P1	33.8	46.6	49.9	56.2	58.5	49.0
P2	12.7	16.0	18.8	16.1	17.1	16.2
DY	53.5	37.4	31.4	27.8	24.4	34.8
P2+DY	66.2	53.4	50.2	43.9	41.5	51.0

Table II. Association Between Parenchymal Pattern,

Age at examination	45-49		50-54		55-59	
Age at first birth	N1+P1	P2+DY	N1+P1	P2+DY	N1+P1	P2+DY
<20	147	152	151	99	131	67
20-32	681	1277	1093	1135	1223	1060
> 32	36	110	77	125	118	137
Nulliparae	83	316	160	341	213	433
	Odds ratio p		Odds ratio p		Odds ratio p	
<20-(20-32)	1.8	xxx	1.6	xxx	1.7	xxx
" >32	3.0	xxx	2.5	xxx	2.3	xxx
" nulliparae	3.7	xxx	3.3	xxx	4.0	xxx
x = p <0.05 xx = p <0.01 xxx = p <0.005						

odds ratios, (Table II) expressing the magnitude of the association between age at examination and the patterns P2 + DY, are found in the right part of the table. Using the age-group 65-69 as a reference group, the odds of having the P2 or DY patterns

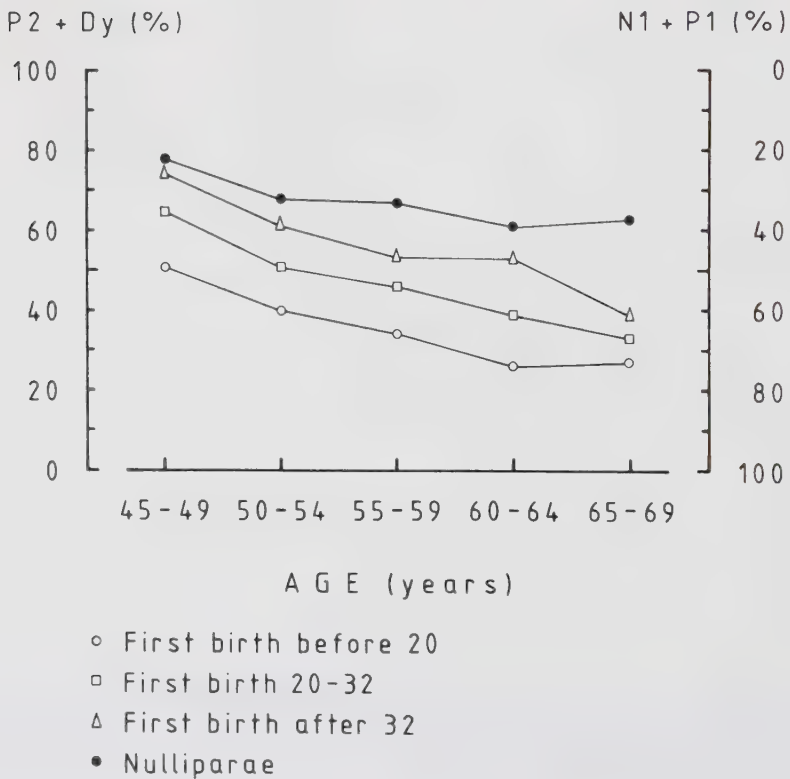
Age at Examination, and Age at First Birth.

60-64		65-69		ODDS RATIO		
N1+P1	P2+DY	N1+P1	P2+DY			
107	38	92	34	(65-69)-(45-49)	2.8	xx
				" (50-54)	1.8	x
				" (55-59)	1.4	n.s.
				" (60-64)	1.0	n.s.
1246	787	983	495	(65-69)-(45-49)	3.7	xxx
				" (50-54)	2.1	xxx
				" (55-59)	1.7	xxx
				" (60-64)	1.3	xx
147	163	230	150	" (45-49)	4.7	xxx
				" (50-54)	2.5	xxx
				" (55-59)	1.8	xxx
				" (60-64)	1.7	xxx
237	370	247	419	(65-59)-(45-49)	2.2	xxx
				" (50-54)	1.3	n.s.
				" (55-59)	1.2	n.s.
				" (60-64)	0.9	n.s.
Odds ratio p		Odds ratio p				
1.8	xxx	1.4	n.s.			
3.1	xxx	1.8	x			
4.4	xxx	4.6	xxx			

varied depending on age at first birth from 0.9 to 1.7 in the age-group 60-64, from 1.2 to 1.8 in the age-group 55-59, from 1.3 to 2.5 in the age-group 50-54 and from 2.2 to 4.7 in the age-group 45-49.

The proportion of mammograms classified as P2 + DY increased with age at first birth and was highest among nulliparae (Fig). The odds ratios, expressing the association between age at first birth and the patterns P2+DY, are found in the lower part of Table II. Using women with first birth before 20 as a reference group, the odds of having the P2 or DY patterns varied depending on age at examination from 1.4 to 1.8 in women with first birth between the age of 20 and 32, from 1.8 to 3.1 in women with first birth after the age of 32 and from 3.3 to 4.6 in nulliparae.

Figure. Parenchymal patterns by age at first birth



DISCUSSION

The present results were obtained in a material covering about 70% of a randomly selected population. As there was no information available on the non-participants it cannot be claimed with certainty that the results are representative of all women aged 45-69. However, no difference was found between the parenchymal patterns of those women who attended the second but not the first screening. Although these women cannot be claimed to be representative of the whole group of non-attenders there is no reason to believe that those initially screened should represent a selected group in terms of parenchymal patterns of the breast.

Factors such as image contrast may influence the classification. A high image contrast can perhaps increase the number of women with breast parenchyma classified as DY. It is also possible that areas of moderate and homogenously increased density are more impressive on film mammograms than on xeromammograms. The various screen-film systems used in the present investigation were apparently equally good for the purpose of classification. The observer variation was 12.9% which agreed well with that reported by Wilkinson et al. (20).

The parenchymal pattern was related to the age of the women (Table I). Although, generally, continuous changes were observed over the whole range of ages studied, the largest changes in the prevalence of the parenchymal patterns occurred around the age of 50, and were thus possibly related to the menopause. The largest change occurred in the prevalence of the DY pattern, which decreased from 53.5% in the 45-49 age-group to 24.4% in the 65-69 group. The prevalence of the other patterns, increased. The increase in the frequency of the P2 pattern was, however, moderate and smaller than that of the N1 and P1 patterns.

Wolfe (23) studied the changes of the parenchymal patterns with age in a material consisting of referred patients who had been examined at least twice at an average interval of 7.6 years. The fact that Wolfe's material was composed of symptomatic women and

that only 153 out of 954 (16%) were above the age of 49, and only 36 at least 60 years of age make any comparison difficult. The largest change found by Wolfe was a decrease with age of the DY pattern, which regressed to the other patterns, above all to the P2 pattern. Most of the changes occurred before the age of 50 and no changes were noted in the small group of patients, 60 years of age or older. Breasts initially classified as N1, P1 or P2 rarely changed.

In our study, the prevalence of the P2 + DY patterns increased within all age-groups with increasing age at first birth and was most frequent among nulliparae. An association between age at first birth and risk of breast cancer has been demonstrated in a worldwide study by MacMahon et al (12) and later confirmed by others (8, 11, 18, 19). MacMahon et al (12) estimated the risk of carcinoma among women with first birth before age 20 to be about 40% of that for women with first birth at 35 or later and 50% of that for nulliparae. However, no such association was found by Shapiro et al. (17) or Adami et al. (3).

Our results are in agreement with those reported by Wilkinson et al. (20), who found a correlation between age at first birth and the DY pattern. However, their material was small ($n = 84$) and the results were not statistically significant.

Rasmussen (15) estimated the degree of "fibroadenosis" from the mammograms of patients hospitalized for diseases other than breast disease and related it to marital status and parity. "Severe fibroadenosis" (probably corresponding to the DY and possibly also to the P2 pattern) was found in 43% of the nulliparae and in 35% of the uniparae. With increasing parity the prevalence decreased to 6% in women with 6 children or more. The material was, however, not stratified for age at examination nor for age at first birth.

The finding in the present material that the P2 + DY patterns showed a co-variation with a rather well established risk factor for breast cancer seems to lend support to Wolfe's suggestion

that women with these patterns represent a high risk group. Wolfe did not correct for potential differences in terms of age at first birth between women with and without breast cancer.

We found the prevalence of the P2 + DY patterns to decrease with advancing age. This is interesting in the light of the reported association between the P2 + DY patterns and cancer and the increasing risk of cancer with increasing age. Whether the observed decreasing prevalence of the P2 + DY patterns represents only the effects of aging or is in part a cohort effect due to differences in exposure to substances that might affect the breast parenchyma, differences in the use of oral contraceptives and other hormone preparations will receive attention at future follow-up examinations of the different age cohorts participating in our mass examination for breast carcinoma now in progress. The increased incidence of breast carcinoma that has been reported by others in patients classified as P2 or DY will furthermore be checked in a prospective study of women without symptoms of breast disease, matched for other factors associated with an increased incidence of breast cancer.

SUMMARY

The mammograms obtained of 15,110 women representing a random selection of all 45 - 69 year old women residing in the town of Malmö and taking part in a screening project for carcinoma of the breast were analysed with the use of Wolfe's criteria for any variation of the pattern of the mammary parenchyma with age and with the woman's age at the birth of her first child.

Judging from the results, the supposed high risk patterns P2 and DY increase in frequency with advancing age of the woman at the birth of her first child and is highest in nulliparae, but decrease with the woman's age at the time of examination.

The predictive power of the P2 and DY patterns for selecting women predisposed to carcinoma of the breast is receiving attention in a prospective investigation in progress at our department.

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From the Departments of Surgery¹, Preventive Medicine² and Diagnostic Radiology², University of Lund, Malmö General Hospital, S-214 01 Malmö, Sweden.

APPRAISAL OF MAMMOGRAPHIC PATTERNS AS MARKERS OF RISK OF BREAST
CANCER

A cross-sectional population study

Lars Janzon¹. M.D., Ingvar Andersson², M.D. and
Holger Pettersson², M.D.

The radiographic appearance of the breast can, according to Wolfe, be classified into four groups termed N1, P1, P2 and DY (1 - 2). This classification system is based on the amount of linear and nodular densities, "prominent duct pattern", and confluent densities in relation to tissue with density of fat. In the N1 group the breast consists almost entirely of fat. In the P1 group a prominent duct pattern occupies at most 25 % of the breast volume; in the P2 group, more than 25 %. The DY group is characterized by confluent densities with or without co-existing prominent duct pattern. In its most extreme form the DY breast is homogenously dense.

According to Wellings and Wolfe (3), the linear and nodular densities correspond to ducts and lobules with periductal and perilobular fibrosis, while the confluent densities represent generalized fibrosis. They also graded and quantified intraductular and intralobular epithelial cell hyperplasia and atypia, which is considered a premalignant lesion (4-7), and compared these variables with the mammographic pattern. In the N1 group no epithelial proliferation or atypia was found. When comparing the P1, P2 and DY groups they found a successive increase in the amount of intraductular and intralobular epithelial cell proliferations and degree of epithelial cell atypia. However, Moskowitz et al (7-8) found no correlation between bland fibrocystic disease, hyperplastic disorders and mammographic parenchymal patterns.

In a cohort study Wolfe (1) found that the P2+DY patterns, as compared with the N1+P1 patterns, were associated with a 6-fold increased risk of breast cancer. Although later results have not been unequivocal (9, 10, 11, 12), several investigators have in general confirmed that, at least in women below 55 years of age the P2 and DY patterns are associated with a moderately increased risk of breast cancer (13, 14, 15, 16, 17).

Wolfe claimed that the P2 and DY patterns could be used as a risk factor for identifying women most susceptible to breast cancer and that selective follow-up of high-risk women after an

initial screening would be possible on the basis of this risk factor. Wolfe's and others' results have, however, been based on findings in women seeking medical advice because of breast complaints or on self-selected women participating in breast cancer detection programs. Whether a certain risk factor can be used as a predictor of breast cancer has to be tried out in the setting where it is to be used, that is, in the general female population.

The aim of the present cross-sectional population study was to assess the relative and attributable risks of breast cancer associated with the P2 and DY patterns.

MATERIAL AND METHODS

The breast cancer screening project now going on in the city of Malmö, Sweden, was started in 1977 in order to assess the effect of mammographic screening on breast cancer mortality. Fifty per cent of all 45-69 year old women (birth cohorts 1908-1932) living in Malmö were randomly selected from the city council register and invited to breast cancer screening examination. Mammography was the only screening method. Two views, cranio-caudal and oblique, of each breast were obtained. Various screen-film systems were used. Most of the examinations were performed with Kodak Min-R. The mammograms were coded according to Wolfe (1-2) by one of three radiologists all of whom had long experience in mammography. Apart from the ages and names of the women no further data were available to the radiologists.

Malmö may be regarded as a closed population area with only one general hospital. All patients with breast cancer are seen at the Department of Oncology and at the Department of Surgery. Hence, it is possible to get a complete coverage of breast cancer cases diagnosed in the city. All 18 women in the non-participating group with breast cancer diagnosed within one year of invitation to screening were traced. In 12 of these the mammographic code was based on findings in the non-cancerous breast. In the re-

maining the code was based on findings in the cancerous breast either because of bilateral disease or because of previous mastectomy for breast cancer.

STATISTICAL METHODS

Fisher's exact test was used for comparisons of proportions.

The odds ratio was calculated according to Fleiss (18) and was used to express the magnitude of association between P2 + DY patterns and breast cancer. The attributable risk was calculated according to the method by Levin (19) using the odds ratio as an estimate of the relative risk of breast cancer associated with the P2 and DY patterns.

RESULTS

21,242 women were invited to screening. 15,748 attended, corresponding to an overall attendance rate of 74 %. The attendance rate was 79 % in the 45-49 age-group, 78 % in the 50-59 group and 68 % in the 60-69 group (table 1). Breast cancer was found in 118 women at the first screening, which corresponds to an overall cancer detection rate of 7.5 per thousand. The cancer detection rate increased with age from 4.7 per thousand in the 45-49 year-group to 10.4 per thousand in the 60-69 year-group. The overall cancer detection rate among participants at screening, 7.5 per thousand was more than twice as high as that among non-participants, 3.3 per thousand within one year of the invitation to screening. Data on mammographic code were available in 15,110 individuals. None of the 638 women in whom data on the mammographic code were missing had breast cancer. The P2 and DY patterns were found in 51 % of the participants and in 61 % of the women with breast cancer detected at screening (table 2; $p < 0.05$). In the non-participating group the P2 and DY patterns were found in 12 (66 %) out of 18 patients with breast cancer ($p > 0.05$ when compared to the prevalence of P2 and DY in participants with breast cancer).

The overall prevalence of the P2 and DY patterns in the participating group declined from 66 % in the 45-49 year-group to 52%

Table 1. Total number of women invited, attendance rate, and cancer detection rate. Figures within brackets denote number of patients in whom screening data were complete.

Age group	Total number of women in invited cohort	Participants			
		All	%	Cancer at screening	
				n	rate per thousand
45 - 49	3795	2983 (2802)	79	14	4.7
50 - 59	8938	6985 (6563)	78	44	6.3
60- 69	8509	5780 (5745)	68	60	10.4
45 - 69	21242	15748 (15110)	74	118	7.5

in the 50-59 group and 43 % in the 60-69 group. A decline was also found in women with breast cancer, but in all the age groups the P2 and DY patterns were more common in women with breast cancer than in those without. The relative risk of breast cancer estimated from the odds ratio in women with the P2 or DY patterns compared with women with the N1 or P1 patterns varied from 3.1 in the 45-49 year-group ($p > 0.05$) to 1.3 in the 50-59 year-group ($p > 0.05$) and 1.8 in the 60-69 year-group ($p < 0.05$).

Table 2 Relative and attributable risk of breast cancer associated with the P2 and DY mammographic breast patterns. Figures within brackets denote the percentages of P2+DY and P1+N1, respectively.

Age	Mammo- graphic pattern	Participants in breast cancer screening			Odds ratio	Attributable risk
		All participants	Women without cancer	Women with cancer		
45	P2+DY	1855 (66)	1843	12 (86)	3.1	58%
	P1+N1	947 (34)	945	2 (14)		
49						
50	P2+DY	3397 (52)	3371	26 (59)	1.3	13%
	P1+N1	3166 (48)	3148	18 (41)		
59						
60	P2+DY	2456 (43) ^x	2422	34 (57) ^x	1.8	25%
	P1+N1	3289 (57)	3263	26 (43)		
69						
45	P2+DY	7708 (51) ^x	7636	72 (61) ^x	1.5	20%
	P1+N1	7402 (49)	7356	46 (39)		
69						

^x $p < 0.05$

The overall attributable risk of breast cancer that could be accounted for by the P2 and DY patterns was 20 %. It varied with age from 58 % in the 45-49 year-group to 13 % in the 50-59 year-group and 25 % in the 60-69 group.

DISCUSSION

In the assessment of an association between any particular factor and a disease it is necessary that the patients and the controls are representative of all individuals respectively with and without the disease. Women referred for mammography because of breast complaints (9, 12, 15, 17) and self-selected women in breast cancer detection programs (13, 14, 16) cannot be considered representative of women in the general population. Any association found between breast cancer and the P2 and DY patterns in case control studies can therefore not be regarded as applicable to the general female population unless the patients and the controls are really representative of all with respectively without the disease.

Except for age, the patients and the controls in Wolfe's study (1) consisted of undefined groups selected in an unknown way from an unknown population. Furthermore, there was an obvious overrepresentation of young patients with breast cancer as 61 % were below 50 years of age. In Sweden, approximately 18 % of breast cancer patients are younger than 50 (20). The P2 + DY patterns are more common in young women than in older women (21). Wolfe's controls were not age-matched and part of the association between the P2 and DY patterns and breast cancer in his study can therefore be accounted for by the relatively large number of young patients with breast cancer. Also, the mammographic diagnosis of breast cancer is more difficult in the P2 and DY groups than in the N1 and P1 groups because of a larger amount of dense tissues. In a cohort study of patients with initially negative mammograms diagnostic difficulties in the P2 and DY groups would tend to erroneously increase the incidence of breast cancer in these groups, especially if the follow-up time is short. The median follow-up time in Wolfe's study was 2.5 years. This explanation is supported by Egan (12) who in a cohort study found the P2 and DY patterns to be associated with a 4-fold increased risk of breast cancer when the follow-up time was less than 4 years. However, the appearance of carcinomas after more than 4 years was equally common in the N1 and P1

groups as in the P2 and DY groups. In our study, all the 10 first interval cancers had been classified as P2 or DY at screening. Retrospectively 3 of the malignancies were considered diagnostic failures. A further 3 could be seen but the abnormalities were too uncharacteristic to warrant suspicion of malignancy. In the remaining cases no abnormalities were seen.

Our investigation is based on findings made in women participating in a cross-sectional breast cancer screening project in which mammography was the only screening method. No difference was found between the prevalence of the P2 + DY patterns in participants and non-participants with breast cancer. Hence there is no reason to assume that, in terms of mammographic patterns, the cancer patients detected at screening should not be representative of all women with breast cancer in the invited cohort. As to the representativeness of the control group, we have in an earlier study reported on similar proportions of mammographic patterns in women who attended the second screening but not the first (21). Even if these women cannot be considered representative of all non-attenders, we consider it unlikely that the difference in risk of breast cancer in the P2 + DY groups found in this study and in Wolfe's can be explained by a biased selection of our control group.

We have earlier found the P2 + DY patterns to be more common in young women than in older women and to be more prevalent in nulliparae and in women with late first birth, than in women with their first birth before 20 years of age (21). We also found a larger proportion of nulliparae and women with late first birth in the higher age-groups than in the lower. Breast cancer is known to be associated with advancing age as well as with late first birth (22). In our study the age specific relative and attributable risks have not been corrected for potential differences in age at first birth in women with and without breast cancer. Such correction would probably lead to a further reduction of the observed association between the P2 and DY patterns and breast cancer.

Our conclusion is that in 45-49 year old women the P2 + DY patterns are associated with a moderately increased risk of breast cancer. Selective follow-up after an initial screening of high risk women on the basis of this risk factor will, however, not be feasible as no more than 50-60 % of all cancers in this age group can be attributed to the P2 and DY patterns.

SUMMARY

In a breast cancer screening project in progress in Malmö, Sweden, radiographic patterns of the breast were classified according to Wolfe as N1, P1, P2 or DY.

The P2 + DY patterns were in all age-groups found more frequently in women with than without breast cancer. The strongest association between the P2 + DY patterns and breast cancer was found in 45-49 year old women (Odds ratio: 3.1, $2p = 0.19$; Fisher's exact test).

It is concluded that in 45 - 49 year old women the P2 + DY patterns are associated with a moderately increased risk of breast cancer. Selective follow up of women found to have the P2 or DY patterns at an initial screening will, however, not be feasible as no more than 50-60 % of all cancers in this age group can be attributed to the P2 and DY patterns.

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